COMPARISION OF BOLUS EPHEDRINE, MEPHENTERMINE AND PHENYLEPHRINE FOR THE MANAGEMENT OF HYPOTENSION DURING SPINAL ANAESTHESIA FOR CAESAREAN SECTION - A CLINICAL STUDY

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CHENNAI - 600 003.

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CERTIFICATE

This is to certify that the dissertation entitled, "COMPARISION OF BOLUS EPHEDRINE, MEPHENTERMINE AND PHENYLEPHRINE FOR THE MANAGEMENT OF HYPOTENSION DURING SPINAL ANAESTHESIA FOR CAESAREAN SECTION-A CLINICAL STUDY", submitted by Dr.Balasubramani.B , in partial fulfillment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamilnadu Dr.M.G.R. Medical University, Chennai, is a bonafide record of the work done by him in the Department of Anaesthesiology , Madras Medical College, during the academic year 2005 – 2008.

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CONTENTS

INTRODUCTION

Anaesthesia to a parturient is not only unique but also requires highest degree of care because the anesthesiologist has to look after two individuals, the mother and foetus. In elective caesarean section under spinal anaesthesia hypotension has been reported in as many as 85% of patients [1].

Hypotension during spinal anesthesia for caesarean delivery can have detrimental effects on both mother and neonate. These effects include decreased utero placental blood flow, impaired foetal oxygenation with asphyxial stress and foetal acidosis and maternal symptoms of low cardiac output such as nausea, vomiting, dizziness and decreased consciousness. Therefore there has been much attention in the literature to methods of preventing and treating hypotension in obstetric anaesthesia. Careful positioning with left uterine displacement and volume preloading with crystalloids or colloids has been used to prevent it, but these are not complete measures [2, 3] and vasopressor is required to correct hypotension quickly.

Vasopressor like Ephedrine, Mephentermine, Phenylephrine, Metaraminol and Methoxamine are used for treating the hypotension. In this study we compare the efficacy of Ephedrine, Mephentermine and Phenylephrine in treating the hypotension for caesarean section and their undesirable side effects.

AIM OF STUDY

To compare the effects of Ephedrine, Mephentermine and Phenylephrine in the management of hypotension during spinal anesthesia for cesarean section based on the following parameters

1. Efficacy of vasopressor in treating hypotension,
2. Incidence of undesirable side effects,
3. Effect on neonatal outcome.

SPINAL ANAESTHESIA

Spinal (subarachnoid/intrathecal) anaesthesia is a form of central neuraxial Block in which a temporary interruption of nerve transmission is achieved following injection of local anaesthetic and/or adjuvant solutions into the subarachnoid space. Spinal anaesthesia is one of the most frequently employed methods of regional anaesthesia.

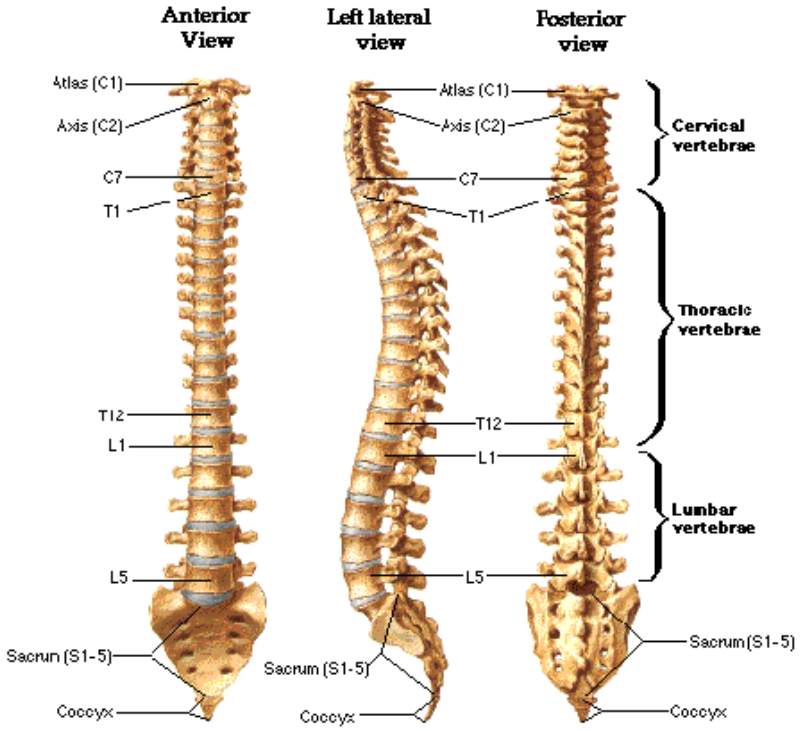
Anatomy:

The vertebral canal extends from the foramen magnum to the sacral hiatus. It is formed by the dorsal spine, pedicles and lamina of successive vertebrae (7 cervical, 12 thoracic, 5 lumbar and 5 sacral). The vertebrae are held together by a series of overlapping ligaments namely the anterior and posterior longitudinal ligaments, ligamentum flavum, interspinous ligament, supraspinous ligament and the intervertebral discs.

The spinal cord, a direct continuation of the medulla oblongata begins at the upper border of the atlas and terminates distally in the conus medullaris. The distal termination, because of the differential growth rates between the bony vertebral canal and central nervous system varies from L3 in the infant, to the lower border of L1 in the adult.

Surrounding the spinal cord in the bony vertebral column are three membranes (from within to the periphery), the piamater, arachnoid mater and dura mater. The pia mater is a highly vascular membrane that closely invests the spinal cord. The arachnoid mater is a delicate vascular membrane closely attached to the outermost dura mater. Between the two innermost membranes is the subarachnoid space. In this space are the cerebrospinal fluid, spinal

FIGURE 1: GENERAL CONFIGURATION OF VERTEBRAL COLUMN



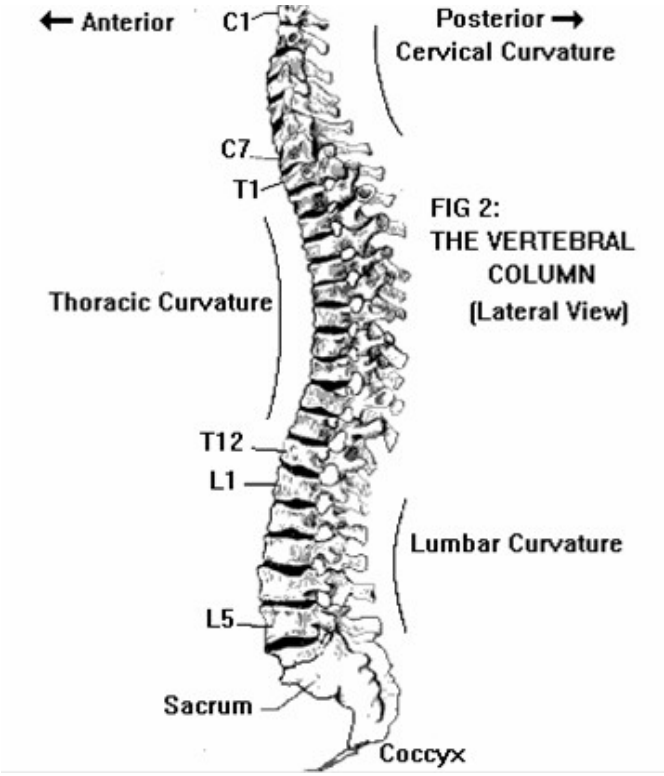
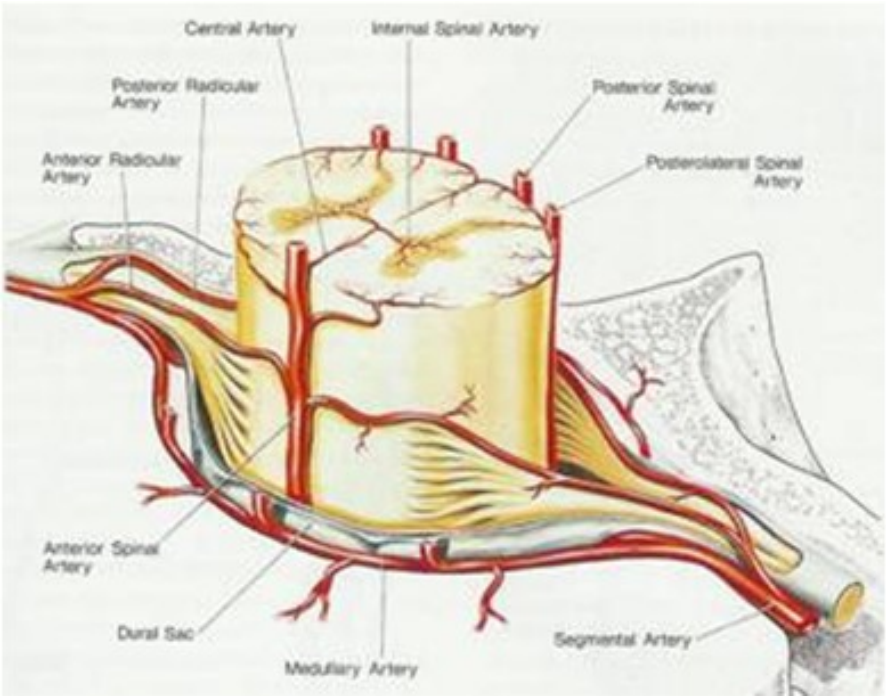


FIGURE 3: ARTERIAL SUPPLY OF THE SPINAL CORD



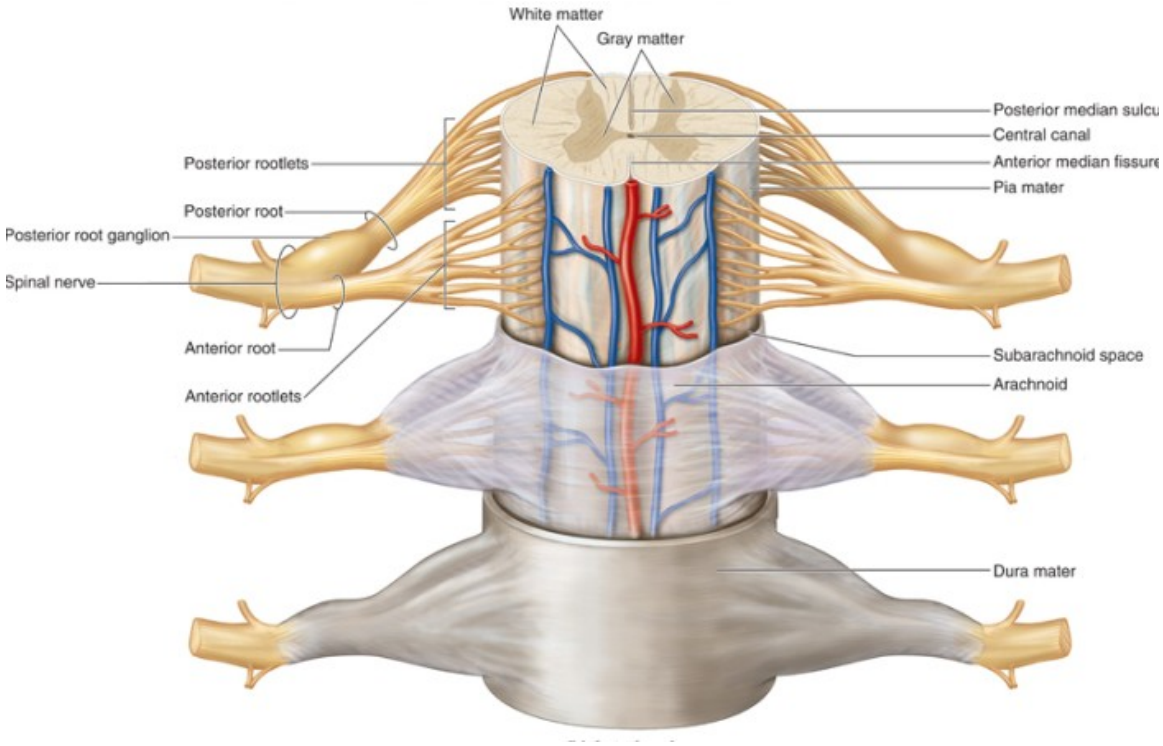
nerves, blood vessels that supply the spinal cord and the denticulate ligaments. Although the spinal cord ends at the lower border of L1 in adults, the subarachnoid space continues to S2. The outermost membrane in the spinal canal is the longitudinally organized fibro elastic membrane, the duramater. This layer is the direct extension of the cranial dura mater and extends as the spinal dura mater from the foramen magnum to S2, where the filum terminale (an extension of the pia mater beginning at the conus medullaris) blends with the periosteum of the subdural space which contains only small amounts of serous fluids to allow the dura and arachnoid move over each other. Surrounding the dura mater is the epidural space which

extends from the foramen magnum to the sacral hiatus. Posterior to the epidural space is the ligamentum flavum which extends from the foramen magnum to the sacral hiatus. Immediately posterior to the ligamentum flavum is the interspinous ligament. Extending from the external occipital protuberance to the coccyx, posterior to these structures is the supraspinous ligament. Lumbar puncture is routinely done below the L2 vertebrae down to the L5-S1 interspace to avoid damaging the spinal cord which ends at the lower border of L1 in adults.

Physiology of subarachnoid block:

The cerebrospinal fluid (CSF) is an ultra filtrate of blood plasma with which it is in hydrostatic and osmotic equilibrium. It is a clear, colourless fluid found in the spinal and cranial subarachnoid space and in the ventricles of the brain. The average volume in the adult ranges from 120-150 ml of which 35 ml is in the ventricles, 25 ml is in the cerebral subarachnoid space and 75 ml is in the spinal subarachnoid space. It is secreted by the choroid plexus at a rate of 0.3-0.4 ml/minute.

FIGURE 4: SPINAL CORD ANATOMY



Physical Characteristics of Cerebrospinal Fluid [4]:

pH	7.4
Specific gravity (H_20) At body temperature At 4°C	 1.007 1.0003
Density	1.0003 g/ml
Baricity	1.000
Pressure	8-12 mm Hg/70-80 mm H2O
Cells	3-5/cu.mm
Proteins	20 mg/dl
Glucose	45-80 mg/dl

The cerebrospinal fluid plays an important role in spinal anaesthesia as media for dispersion of the local anaesthetic drug to the spinal nerve. An important factor determining the spread of drugs in the subarachnoid space is the specific gravity of the injected solution compared with that of CSF.

Mechanism of Spinal Anaesthesia:

Injection of local anesthetic solution into the spinal CSF allows access to sites of action both within the spinal cord and the peripheral nerve roots. The nerve roots leaving the spinal canal are not covered by epithelium and are readily exposed to the local anesthetic within the CSF. Therefore afferent impulses leaving via the ventral nerve roots are blocked during spinal anesthesia. Local anaesthetics block sodium channels and electrical conduction in spinal nerve roots. There are also multiple potential actions of local anesthetics within the spinal cord at different sites. Local anaesthetics

FIGURE 5: DERMATOMAL CHART

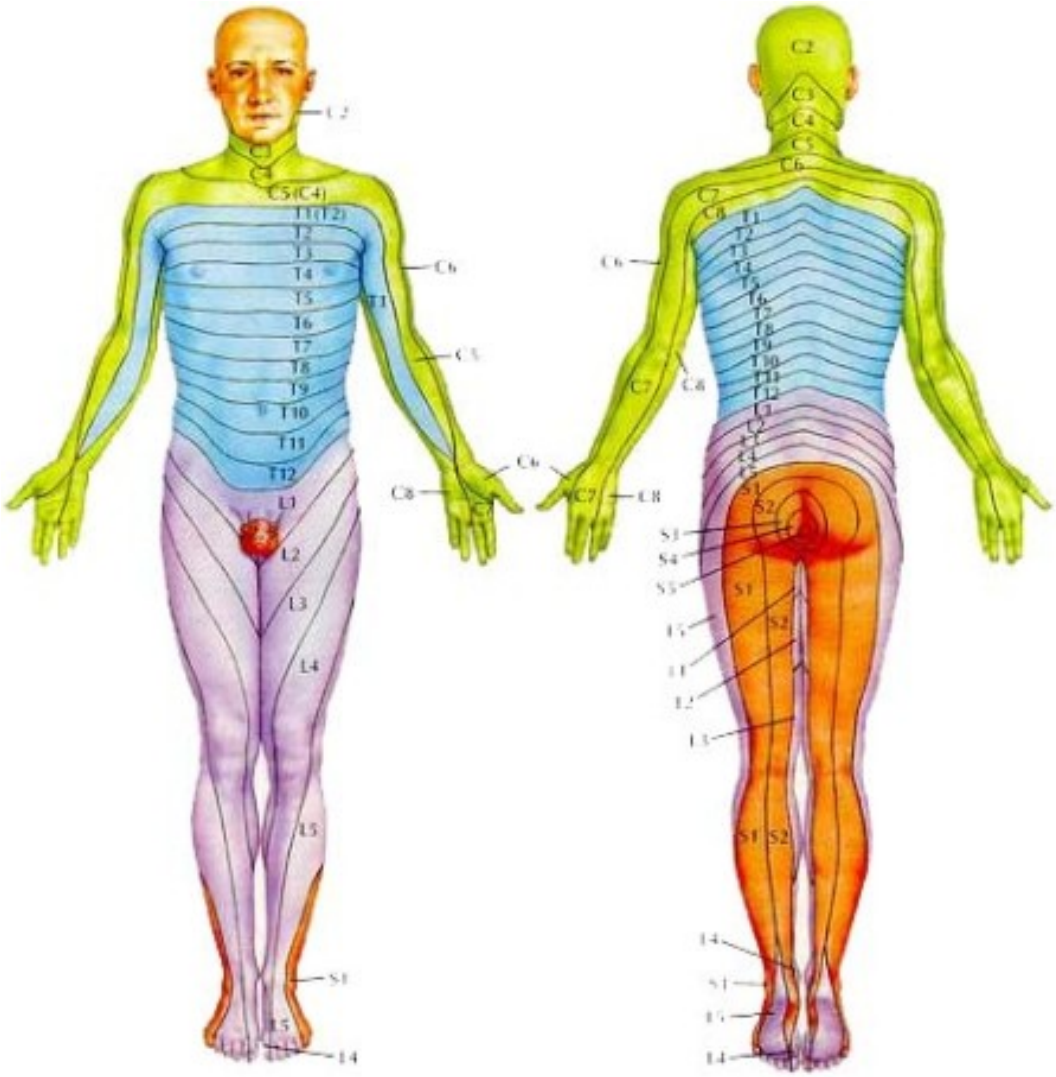
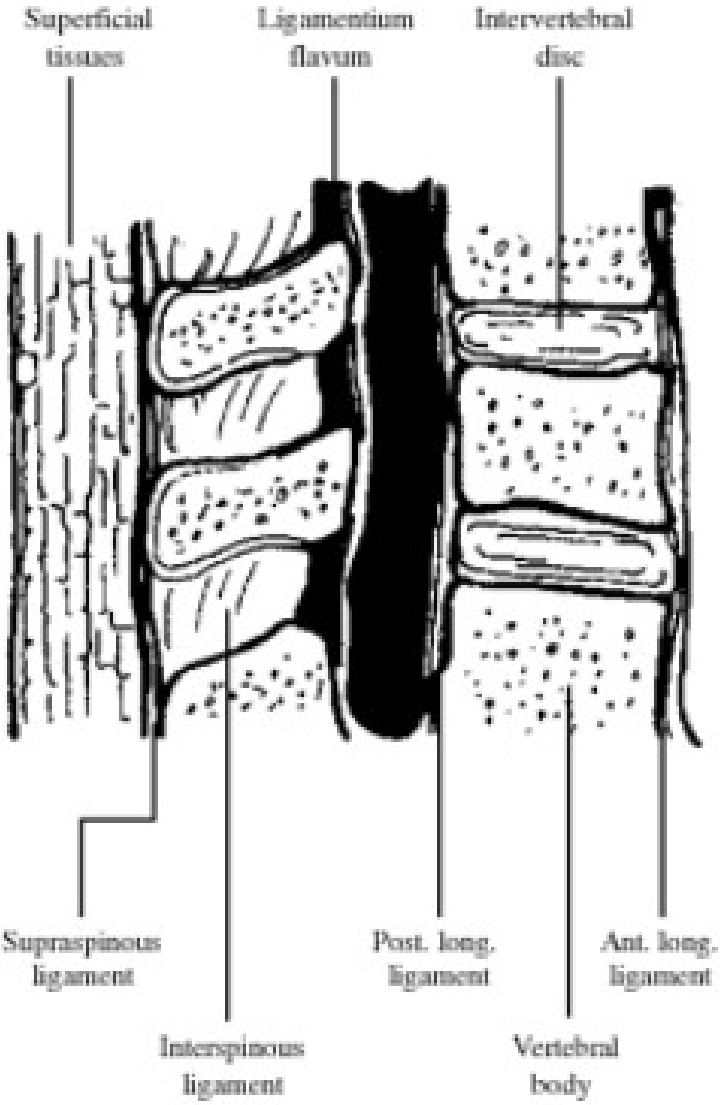


FIGURE 6:SUBARACHNOID BLOCK-RELATIONS



can exert sodium channel block with in the dorsal and ventral horns, inhibiting generation and propagation of electrical activity [5].

Zone of Differential Blockade:

Sensory: In Subarachnoid block, sympathetic fibers are two to three segments higher than sensory fibers. Sympathetic block will be greater when more concentrated solutions are used or when adrenaline is added, as this has a similar effect.

Motor: In Subarachnoid block, the difference between sensory and motor block is slight (Two segments).

Order of blocking nerve fibers:

1. Autonomic preganglionic β fibers.
2. Temperature fibers- Cold before warm.
3. Pinprick fibers.
4. Fibers conveying pain greater than pin prick.
5. Touch fibers.
6. Deep pressure fibers.
7. Somatic motor fibers.
8. Fibers conveying vibratory sense and proprioceptic impulses.

During recovery, return of sensibility in the reverse order was assumed, but it has been suggested that sympathetic activity returns before sensation.

Spread of Local Anaesthetics in subarachnoid space:

The local anaesthetic solution is diluted by CSF and therefore its original concentration is of less moment than the actual mass of drug injected. Spread is also determined by the baricity of the injected solution. Baricity is a ratio comparing the density of a local anesthetic solution at a specified temperature to the density of CSF at the same temperature. A hypobaric solution has a baricity less than 1.0000 or specific gravity less than 1.0069(the

mean value of specific gravity). A hyperbaric solution has a baricity greater than 1.0000 or specific gravity more than 1.0069. Hypobaric and Hyperbaric solutions are prepared from isobaric solutions by the addition of various amounts of sterile distilled water and dextrose respectively. Isobaric solutions do not move under the influence of gravity in the CSF. Hyperbaric solutions, being heavier than CSF, settle to the most dependent aspect of the subarachnoid space, which is determined by the position of the patient. In supine patient, hyperbaric solutions gravitate to the thoracic kyphosis. Hypobaric solution floats up to the nerves innervating the surgical site. The major factors affecting height of the block are the baricity of the local anaesthetic solution and the dosage of drug injected.

Fate of Local Anaesthetics in Subarachnoid Space:

Following injection of local anaesthetic solution into subarachnoid space, its concentration falls rapidly. The initial steep fall is due to mixing with CSF and subsequent absorption into nerve roots and spinal cord. The regress of local anaesthetic solution following subarachnoid injection is primarily by vascular absorption with no hydrolysis or degradation taking place in the CSF. Depending on the type of the drug used, it is metabolized in plasma by pseudo cholinesterase or in the liver. As duration of anaesthesia is in the part, a result of the rate of absorption from the subarachnoid space, the addition of a vasoconstrictor to the local anesthetic solution will retard absorption of the drug and thus increase the duration of anaesthesia.

Indications for subarachnoid block:

Spinal anaesthesia can be administered whenever a surgical procedure can be done with a sensory level of anesthesia that does not produce adverse patient outcome which includes

- Lower abdominal surgeries,

- Lower limb surgeries,
- Urological procedures,
- Obstetric procedures,
- Gynecological surgeries,
- Perineal and rectal surgeries.

Contraindications for subarachnoid block:

Absolute contraindication:

- Patient refusal,
- Local sepsis.

Relative contraindications:

- Uncorrected coagulopathy,
- Uncontrolled blood loss/shock,
- Fixed cardiac output states,
- Documented allergy to local anesthetics,
- Raised intracranial pressure,
- Neurological disease,
- Major spine deformities/previous surgery on the spine,
- Severe cardiac disease.

Circulatory effects of subarachnoid block [6]:

There are six different ways in which subarachnoid block can influence the cardiovascular system.

1) Vasodilatation of resistance and capacitance vessels.
2) Block of cardiac efferent sympathetic fibers from T1 to T4 resulting in loss of chronotrophic and inotrophic drive and fall in cardiac output.
3) The atrial or Bainbridge reflex causing bradycardia.
4) The operation of Marey's law causing tachycardia.

5) Depression of vascular smooth muscle and β-adrenergic blockade of myocardium with fall in cardiac output, following systemic absorption of the local anesthetic drug.
6) Adrenaline effect (if used), following absorption, resulting in β stimulation and associated rise in cardiac output and reduction in peripheral resistance. The overall effect is likely to be a greater fall in mean arterial pressure than if adrenaline had not been used.

Slowing of heart rate is caused if any of the anterior roots carrying sympathetic cardiac accelerator fibers are blocked, as may happen in high spinals above T4-5.

A further cause of slow pulse rate is the lowering of blood pressure in the right atrium consequent on diminished venous return (Bain Bridge reflex).

SPINAL ANAESTHESIA-TECHNIQUE

The first step in the successful application is proper patient selection. This is accomplished by evaluation of the patient through history, physical examination, laboratory data and communication with the patient and surgical staff about details of the procedure. Suitable premedication is given to the patient before performing the subarachnoid block. Reliable intravenous access through a large bore intravenous cannula is mandatory. The administration of 500-1000 ml of crystalloid or colloid to limit the hypotension that may result from the sympathetic block produced by spinal anesthesia has some merit. The recommended standards for airway management and emergency drugs are kept in readiness. Spinal anaesthesia should be administered to a cooperative patient who is placed on a table that can be tilted upward or downward.

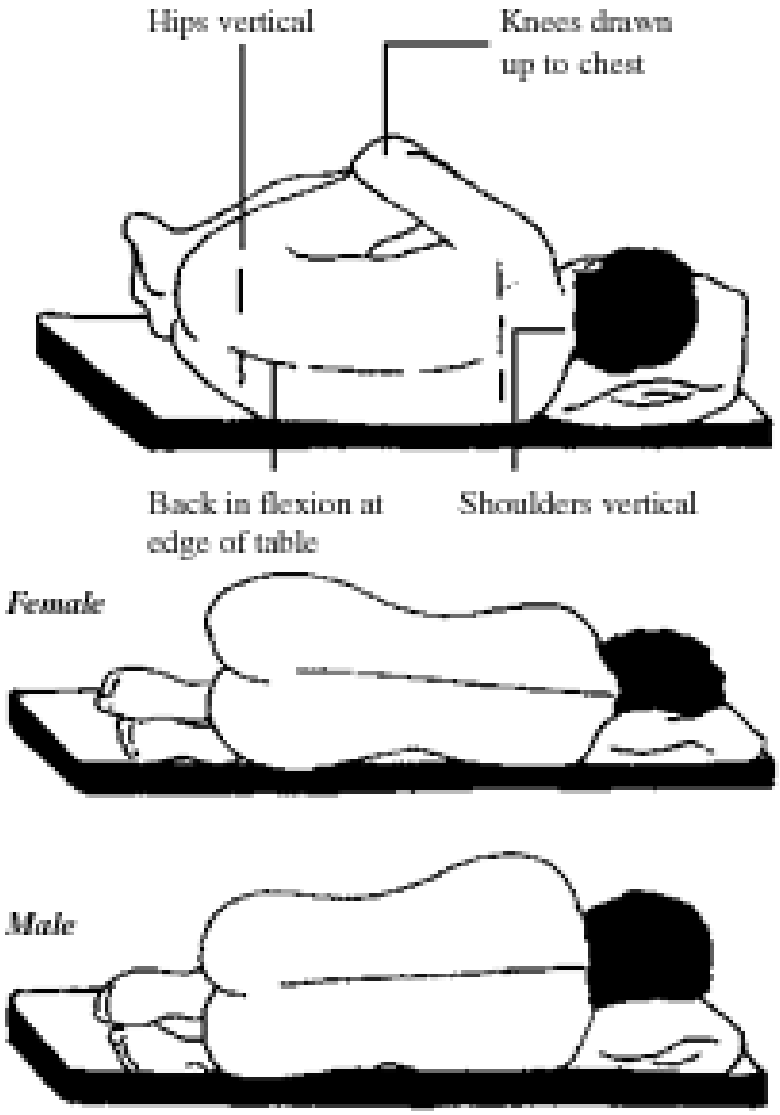
Procedure:

The spinal anaesthetic technique can be broken down into a series of steps, the four P`s; Preparation, Position, Projection and Puncture. [7, 8]

Preparation:

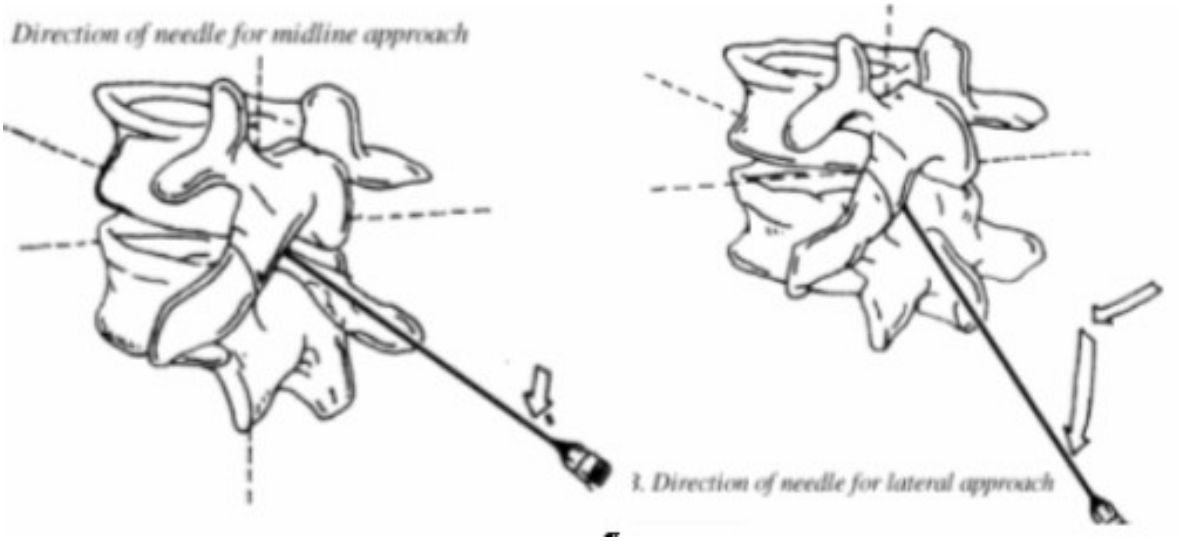
Preparation of the equipment and drugs is essential for performing a subarachnoid block. The choice of drug is based on the duration of block desired, the surgical procedure and patient variables. Spinal needles of various diameters with various types of points are available. Spinal needles fall into two main categories; those that cut the dura and those that designed to separate the dural fibers. The former includes the Quincke-Babcock needle and the latter include the Greene, Whitaker and Sprotte needles. In order to

FIGURE 7: SPINAL ANAESTHESIA-POSITIONING



Note how the level of the subarachnoid space varies between male and female

FIGURE 8: SPINAL ANAESTHESIA-TECHNIQUE



keep the incidence of post dural puncture headache to a minimum, small bore needles with a rounded non cutting bevel are preferred.

Position:

The choice of position of the patient for performing the subarachnoid block depends on a number of factors, the proposed surgery being the most important. The three primary methods of positioning include lateral decubitus, sitting and prone positions, each with its own advantages in specific situation. In the lateral decubitus position, the patient is placed with his/her back parallel to the edge of the operating table nearest the anaesthesiologist, with thigh flexed upon the abdomen and neck flexed to allow the forehead to be as close to the knees as possible. The sitting position is chosen when low lumbar and sacral levels of anaesthesia are adequate for the surgical procedure, when obesity or scoliosis make identification of midline anatomy difficult in the lateral decubitus position or when orthopedic problems of the hip and knee exist. The prone position is used primarily for the hypobaric technique for rectal and perineal procedures.

Projection and puncture:

The spinal puncture can be performed either by a midline or a Para median approach, usually at the L2-L3, L3-L4, or L4-L5 interspaces. The procedure is carried out under strict aseptic conditions. The patients back is widely prepared with an antiseptic solution and sterile drapes applied. A line from the highest point of iliac crest passes through either the spinous process of L4 or the L3-L4 interspace. Traditionally the midline approach with patient

in lateral decubitus position is most popular. Depending on the interspace and approach selected, a subcutaneous skin wheal is raised over the intended puncture site with local anesthetic solution. If an introducer is not used, the skin and soft tissues are fixed against the bony landmarks which straddle the interspace by the second and third fingers of the non dominant hand of the anaesthesiologist. The needle is inserted in midline in the middle of the interspace with the bevel parallel to the longitudinal dural fibers. After traversing the skin and subcutaneous tissue, the needle is advanced in a slightly cephalad direction with the long axis of the vertebral canal. A characteristic change of resistance occurs as the needle traverses the supraspinous ligament, interspinous ligament, ligamentum flavum, dura and pierces the arachnoid which becomes quiet recognizable as experience is gained. The stylet is removed and appearance of cerebrospinal fluid at the hub of the needle confirms the correct position of needle tip. The hub of the needle is held firmly between the thumb and index finger of the anaesthesiologist's non-dominant hand and the back of that hand is placed against patients back to steady the needle, while syringe containing anaesthetic solution is firmly attached to the needle.

After confirming free flow of spinal fluid by aspiration, the anaesthetic solution is injected. The patient is placed in desired position. Cardiovascular and respiratory functions are monitored. Analgesia is checked by loss of sensation to pin prick.

PHYSIOLOGICAL CHANGES DURING PREGNANCY [9, 10]

Marked anatomic and physiologic changes occur in women during pregnancy.

Body weight and composition:

The mean weight increase during pregnancy is 17% of prepregnant weight (12 kg approximately).

This increase results from:

-Increase in size of the uterus and its contents:

-Uterus : 1 kg,

-Amniotic fluid : 1 kg,

-Fetus and placenta: 4 kg.

-Increase in Blood volume and interstitial fluid: 2 kg each

-Deposition of new fat and protein: 4 kg.

1st Trimester	1-2 kg
2nd Trimester	5-6 kg
3rd Trimester	5-6 kg

-Weight gain:

Metabolism and respiration:

Oxygen consumption:

- Increases by 30% to 40% during pregnancy.
- Progressive rise is caused by metabolic needs of fetus, uterus and placenta and secondarily by increased cardiac and respiratory work.

Anatomy:

- The thoracic cage increases in circumference by 5-7 cm during pregnancy because of both increase in both anteroposterior and transverse diameter.
- Capillary engorgement of nasal, orapharangeal mucosa, larynx begins early in the first trimester and increases progressively throughout pregnancy.
- Airway conductance increases, indicating dilatation of larger airways below the larynx. Factors contributing to airway dilatation include direct effects of progesterone, cortisol, relaxin and enhanced β adrenergic activity induced by progesterone.
- Diaphragm excursion is increased and chest wall excursion is decreased.

Lung volumes and capacities:

- Tidal volume increases by 45% during pregnancy with half occurring during 1^{st} trimester.
- FRC begins to decrease by 5^{th} month and is decreased to 80% of nonpregnant values by term gestation.
- 25% reduction in expiratory reserve volume and 15% reduction in residual volume.

Lung volumes	Change
Inspiratory reserve volume	+5%
Tidal volume	+ 45%
Expiratory reserve volume	- 25%
Residual volume	- 15%

Lung capacities	Change
Inspiratory capacity	+15%
Functional residual capacity	-20%
Vital capacity	No change
Total lung capacity	-5%
Dead space	+45%
Respiratory rate	No change
Ventilation:	
Minute ventilation	+45%
Alveolar ventilation	+45%

Ventilation:

Minute ventilation increases by 45% during pregnancy with an increase evident early in the first trimester. This change results from the increase in tidal volume. Although respiratory rate declines slightly during midgestation, it is essentially unaltered during pregnancy.

The ratio of dead space to tidal volume does not change during pregnancy and the increase in alveolar ventilation is equivalent to minute ventilation throughout the gestation. Progesterone increases the sensitivity of central respiratory centre to CO_2 and acts as a direct respiratory stimulant. Estrogen also contributes to increased ventilation.

Anaesthetic significance of respiratory changes:

1. Airway management is more challenging
    - Weight gain and breast engorgement hinder laryngoscopy.
    - Swollen mucosa bleeds easily; to avoid intranasal manipulation.
    - Use smaller endotracheal tube (6-7mm).

2. Response to anesthetics
    - MAC decreased.
    - Decreased FRC results in faster induction with insoluble agents.
    - Increased VE speeds induction with soluble agents.
    - Rapid overdose with loss of airway reflexes.
3. Greater risk of hypoxemia.
    - Decreased FRC means less oxygen reserve.
    - Increased oxygen consumption. Rapid airway obstruction.
4. Excessive mechanical hyperventilation ($P_{ET}Co_2$<24) may reduce maternal cardiac output and uterine blood flow.
5. Maternal and fetal hypoxemia is associated with pain induced hypo and hyper ventilation; can be avoided with effective analgesia.

The Heart and circulation:

Examination:

Elevation of diaphragm shifts the heart anteriorly and to the left during pregnancy. The apical impulse moves cephalad to fourth intercostal space and laterally to the midclavicular line.

On auscultation accentuation of S1 with exaggerated splitting of S1 occurs. S2 is changed a little and S3 is easily heard during the later half of pregnancy. Grade I or II early to mid systolic murmur is commonly heard at

the left sternal border and is attributable to cardiac enlargement which results in dilatation of tricuspid annulus that causes regurgitation.

ECG: Reveals sinus tachycardia with shortening of PR and uncorrected QT intervals during pregnancy. QRS axis shifts to right during first trimester but shifts to left during third trimester.

Central hemodynamics:

Cardiac output increases from the 5^{th} week after the last menstrual period and 35% to 40% increase by the end of first trimester. Rise throughout the second trimester to reach a maximum of 50% greater than that of non pregnant women and does not change during the reminder of pregnancy. Heart rate starts to increase by 4^{th} to 5^{th} week of pregnancy. Rises approximately 15% to 25% above the nonpregnant values by the end of first and second trimester and no further changes in the third trimester. Stroke volume increases approximately 20% between 5^{th} and 8^{th} week of gestation, increases by 25% to 30% by the end of second trimester and remains the same.

Organ perfusion:

Uterine blood flow estimated to be from 50-190ml/mt before conception, increases to 700-900ml/mt at term. 90% of this flow peruses the intervillous space and 10% to the myometrium. Renal plasma flow is increased by 80% at 16-20 weeks but declines to 50% above the nonpregnant level at term. Skin perfusion begins to increase by 15 weeks and at term increases three to four times to nonpregnant level.

Blood pressure:

Systolic blood pressure is minimally affected by pregnancy, with a maximum decline of approximately 8% during early to midgestation and return to prepregnant level at term. Diastolic blood pressure falls to a greater degree with early to mid gestational decrease of approximately 20%. It also returns to prepregnant level at term.

Hemodynamics during labour:

Cardiac output during labour (between uterine contractions) increases from prelabour values by approximately 10% in early first stage, 25% in late first stage and 40% in second stage. These changes results from increase in stroke volume with minimal changes in heart rate. Systolic and diastolic blood pressures are also elevated during late first stage and second stage of labour .A progressive elevation of sympathetic nervous system activity accounts for these changes by increasing myocardial contractility, systemic vascular resistance and venous return.

Suppression of sympathetic nervous system activity with epidural analgesia reduces the increase in cardiac output during labour. Cardiac output and stroke volume are augmented by an additional 15% to 25% during uterine contractions with lesser increase of 10% to 15% when parturients receive effective analgesia.

Parameter	Change
Cardiac output	+50%
Stroke volume	+25%
Heart rate	+25%
Left ventricular end diastolic Volume	Increased
Left ventricular end systolic Volume	No change
Ejection fraction	Increased
Left ventricular stroke work index	No change
Pulmonary capillary wedge pressure	No change
Pulmonary artery diastolic pressure	No change
Central venous pressure	No change
Systemic vascular resistance	-20%

Anaesthetic significance of cardiovascular changes:

1. Venodilatation may increase the incidence of accidental epidural vein puncture.
2. Healthy parturient will tolerate up to 1500 ml blood loss. Transfusion is rarely required.
3. Oxytocin with a free water IV infusion may lead to fluid overload.
4. High hemoglobin level (>14gm %) indicates low volume state caused by preeclampsia, hypertension, or inappropriate diuretics.
5. Cardiac output remains high in first few hours postpartum; women with cardiac or pulmonary disease remain at risk after delivery.
6. Epidural block reduces cardiac work during labour and may be beneficial in some cardiac disease states.
7. Always avoid aortocaval compression: 70-80% of supine parturients with a T4 level develop significant hypotension.

Haematology:

The changes that occur during pregnancy are given as follows:

At term:

Blood volume	+45%
Plasma volume	+55%
RBC volume	+30%
Hemoglobin	11.6gm%
Hematocrit	35.5%

Gastrointestinal system:

Stomach is displaced upwards towards the left side of the diaphragm during pregnancy. This displaces intraabdominal portion of esophagus into the thorax leading to reduction in tone of lower esophageal high pressure zone (LEHPZ). This causes pyrosis (heart burn) as a result of reduced barrier pressure (LEHPZ-IGP).

PHARMACOLOGY [11, 12]

EPHEDRINE

Ephedrine is a synthetic, sympathomimetic, noncatecholamine drug primarily used as a vasopressor in various clinical situations.

Pharmacodynamics:

Ephedrine has direct effects on α, $ß_1$ and $ß_2$ receptors and indirect effects by releasing endogenous nor epinephrine from synaptic storage sites. Ephedrine causes increase in systolic and diastolic blood pressure, heart rate and cardiac output. Renal and splanchnic blood flows are decreased, whereas coronary and skeletal muscle blood flows are increased. Systemic vascular resistance may be altered minimally because vasoconstriction in some vascular beds is offset by vasodilatation ($ß_2$ stimulation) in other areas. These cardiovascular effects are due, in part, to α receptor mediated peripheral arterial and venous vasoconstriction. The principal mechanism, however for cardiovascular effects produced by ephedrine is increased myocardial contractility due to activation of $ß_1$receptors. In the presence of preexisting ß adrenergic blockade, the cardiovascular effects of ephedrine may resemble responses more typical of α adrenergic stimulation.

Pharmacokinetics:

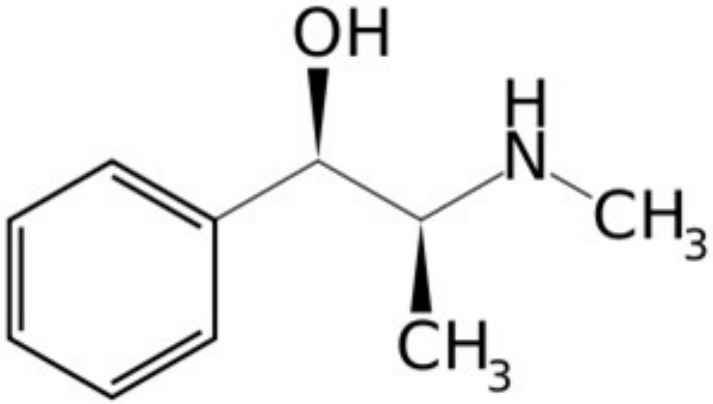
	PO	**IM**	**IV**
Onset of action:	15-60 mts,	10-20mts,	1-2 mts,
Duration of action:	3-5hrs,	30-60mts,	15-30mts.

Ephedrine is excreted mostly as unchanged drug in urine. The rate of excretion is dependent on urinary pH. Excretion is increased in acidic urine.

Ephedrine is resistant to metabolism by MAO in the gastro intestinal tract, thus permitting unchanged drug to be absorbed into circulation after oral

EPHEDRINE

CHEMICAL STRUCTURE



administration. Intramuscular injection of Ephedrine is also acceptable because drug induced local vasoconstriction is insufficient to greatly delay systemic absorption.

Some Ephedrine is deaminated by MAO in the liver and conjugation also occurs. The slow inactivation and excretion of Ephedrine are responsible for the prolonged duration of action.

Indication:

- As a vasopressor to treat hypotension caused by sympathetic nervous system blockade or hypotension due to inhaled or injected anesthetics.
- As a vasopressor in shock.
- As a chronic oral medication to treat bronchial asthma.

- Nasally as nasal decongestant to treat vasomotor rhinitis, acute sinusitis, hay fever and acute coryza.
- As an antiemetic.

Contraindication:

- Angle closure glaucoma, Thyrotoxicosis.
- Obstetrics when maternal BP is >130/80.

Precaution:

- Geriatric patients may be at a higher risk to develop prostatic hypertrophy.
- In patients with coronary insufficiency or IHD, hypertension may cause intracranial hemorrhage or angina pain.

Side effects:

- CNS: Nervousness, confusion, delirium and hallucinations can occur. Anxiety and nervousness may occur after prolonged use.
- CVS: Precordial pain and excessive doses may cause hypertension sufficient to result in intracranial hemorrhage.
- Genitourinary: Difficult and painful urination with urinary retention can occur in males with Prostatism. Also urine formation is decreased.

Dosage and administration:

- Oral: For Bronchial asthma, Systemic Nasal decongestion:
  -12.5-25mg, 4^{th} hourly, not to exceed 150mg in 24hrs.
- Parentral:
  - For Bronchial Asthma:
    Adults: 25-50mg SC or IM,
    5-25 mg slow IV, if needed repeated every 5-10mts.
    Children: 0.5mg/kg SC or IM, 6^{th} hourly.

- Vasopressor:

  Adults: 25-50mg IM, SC,

  5-25mg IV, repeated at 5-10mts intervals

  Children: 0.5mg/kg IM, IV.
- Nasal decongestion: 0.25% Spray, Topically.
- Antiemetic: 0.5mg/kg IM.

Tolerance:

A second dose of Ephedrine produces a less intense systemic blood pressure response than the first dose. This phenomenon known as Tachyphylaxis occurs with many sympathomimetics and is related to the duration of action of these drugs. Tachyphylaxis may also be due to depletion of nor epinephrine stores

MEPHENTERMINE

Mephentermine is a synthetic, sympathomimetic, noncatecholamine drug which is structurally closely related to methyl amphetamine.

Pharmacodynamics:

Mephentermine indirectly stimulates beta adrenergic receptors and possibly to a lesser extent alpha adrenergic receptors of sympathetic nervous system by releasing noradrenalin from its storage sites. The main effect of therapeutic doses of Mephentermine is cardiac stimulation.

Mephentermine produces a positive inotrophic effect on the myocardium. Force of contraction and cardiac output are usually increased and may be accompanied by an increased stroke volume in some patients.

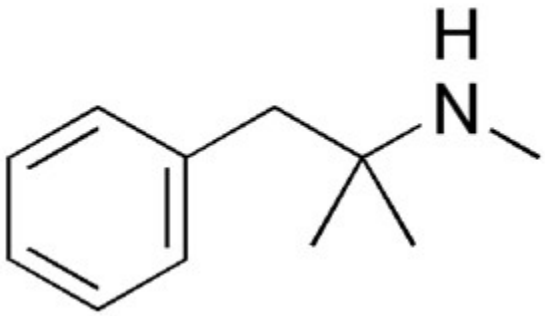
Mephentermine shorten atrioventricular conduction velocity and the refractory period of the AV node and increases ventricular conduction velocity. Although the drug produces a positive chronotrophic effect at the sinoatrial node, this effect is usually overcome by increased vagal activity occurring as a reflex to increased blood pressure. Heart rate may be increased, decreased or unchanged.

Mephentermine directly dilates the arteries and arterioles in the skeletal and mesenteric vascular beds. Venous return to the heart is increased. Also increases systolic and diastolic blood pressure by increasing cardiac output. Increase in cardiac output is greatest when initial cardiac output is low. When cardiac output is high, increased peripheral vascular resistance may be responsible for increase in blood pressure.

Mephentermine also dilates the coronary, cerebral, splanchnic and renal blood vessels and also stimulates central nervous system.

MEPHENTERMINE

CHEMICAL STRUCTURE



Pharmacokinetics:	IV	IM
Onset of action	Immediate,	5-15 mts,
Duration of action	Upto 30 mts.	Upto 4 hrs.

It is rapidly metabolized in the body by demethylation in the liver followed by hydroxylation. It is excreted as unchanged drug and metabolites in urine. Excretion is more rapid in acidic urine.

Indication:

- Hypotension due to anesthesia, ganglionic blockade or hemorrhage.
- Shock accompanying myocardial infarction.

Contraindication:

- To treat hypotension caused by Chlorpromazine.
- In combination with MAO inhibitors.

Precautions:

- Hypoxia, Hypercapnia, Acidosis may reduce the effectiveness of and/or increase the adverse effects of the drug.

Drug interactions:

- The vasoconstrictor effects of Mephentermine may be enhanced by concurrent administration of drugs with similar effects like Ergot alkaloids or Oxytocin.
- Administration of Mephentermine to patients who are receiving cyclopropane or halogenated hydrocarbon general anesthetics may increase cardiac irritability which may result in arrhythmias.

Side effects:

- Anxiety,
- Cardiac arrhythmias,
- Hypertension (especially in those with heart disease).

Dosage and administration:

- Hypotension secondary to spinal anesthesia(Prophylaxis)

IM: 30-45mg, administered 10-20 mts prior to anesthesia, operation or termination of operative procedure.

- Hypotension secondary to spinal anesthesia(Treatment)

IV: 10-25 mg given as a single dose. May be repeated as needed to maintain the desired level of blood pressure.

IV infusion: as 0.1 %(1mg/ml) solution in 5%Dextrose in water, the rate of administration and duration of therapy being adjusted according to patient response.

- Shock accompanying Myocardial Infarction:

An initial dose 60mg IV bolus followed by IV infusion of 0.1%Mephentermine in 5% Dextrose in water or IV administration of serial doses of Mephentermine 30-45mg, as necessary.

PHENYLEPHRINE

Phenylephrine is a synthetic sympathomimetic agent. It is a vasoconstrictor and vasopressor drug chemically related to ephedrine and adrenaline.

Pharmacodynamics:

Phenylephrine is a powerful post – synaptic α_1 receptor stimulant with little effect on ß receptors at the heart. Phenylephrine is a directly acting sympathomimetic agent. After injection it produces pronounced peripheral vasoconstriction and hence increases in both systolic and diastolic BP. Its action on the heart differs from that of adrenaline and ephedrine, in that it slows the heart rate and increases the stoke volume producing no disturbance in rhythm. At therapeutic doses it usually does not cause central nervous system stimulation. A major advantage of Phenylephrine is the fact that repeated administration produces comparable effects.

Also acts on α receptors producing vasoconstriction in the skin, mucus membranes and the mucosa as well as mydriasis by contracting the dilator muscle of the pupil. Cardiac output is slightly decreased and peripheral resistance is considerably increased. Circulation time is slightly prolonged and venous pressure is slightly increased. Venous constriction is not marked. Most vascular beds are constricted. Renal, cutaneous, splanchnic and limb flows are increased. Pulmonary vessels are constricted and pulmonary arterial pressure is raised. Resembles epinephrine, but it has more prolonged action and few cardiac effects.

Pharmacokinetics:	IV	IM,SC	Topical
Onset:	immediate,	10-15mts,	15 - 20mts,
Duration:	15- 20mts,	0.5-2hrs for im, 50-60mts for sc,	30- 40mts

Ophthalmic:

Time to peak effect for mydriasis: 2.5%: 15 – 60mts.

10%: 10 – 90 mts

Duration: 2.5%: 3hrs.

10 %: 5 – 7hrs.

Phenylephrine is metabolized in the liver by monoamine oxidases. The metabolites are excreted in urine.

Indications:

To prevent or treat hypotension during

- Spinal and inhalation anesthetics,
- Shock and shock like states,
- Warm septic shock,
- Drug induced hypotension or hypersensitivity reaction or anaphylaxis,
- Weaning from cardiopulmonary bypass.
- To overcome paroxysmal supraventricular tachycardia (high doses to produce reflex bradycardia)
- To prolong duration of spinal anesthesia with lignocaine.
- As a vasoconstrictor in regional anesthesia

Nasal: Nasal congestion due to allergies, sinusitis, common cold or hay fever

Ophthalmologic: 0.12%, 2.5%, 10%:

- Temporary relief of redness of the eye
- Decongestant and vasoconstrictor
- Treatment of uveitis with posterior synechiae.

- Open angle glaucoma, Retraction without cycloplegia
- Ophthalmic examination, Fundoscopy.

Contraindications:

- Severe hypertension.
- Hyperthyroidism.
- Ventricular tachycardia.

Precautions:

- To be used with extreme caution in geriatric pts, severe arteriosclerosis, bradycardia, partial heart block, myocardial disease, and hyperthyroidism. Anginal pain may be precipitated in pts with angina pectoris.
- To be used with caution in patients with Diabetes mellitus or closed angle glaucoma.

Side effects:

Phenylephrine is without significant stimulating effects on the central nervous system at usual doses

- Extravasations of the drug may cause tissue necrosis.
- CVS: Reflex bradycardia, arrhythmias.
- CNS: Headache, excitability and restlessness
- Ophthalmologic: Rebound miosis and decreased mydriatic response in geriatric patients, blurred vision.

Dosage and administration:

- Mild to moderate hypotension:

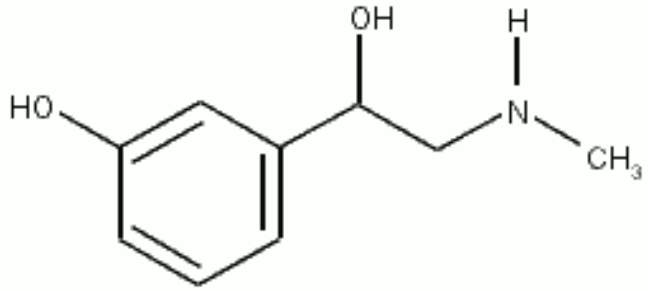
  SC or IM: 2 – 5 mg, initial dose should not exceed 5mg.

  IV: 0.2mg, range from 0.1 – 0.5mg. Initial dose should not exceed 0.5mg.
- Severe hypotension, shock:

IV infusion: 10 mg in 500ml of 5% dextrose start at 100 180µg/min until target BP achieved, and a maintenance rate of 40 - 60µg / min.

PHENYLEPHRINE

CHEMICAL STRUCTURE



- Hypotension due to central neuraxial blockade:

  Prophylaxis: SC or IM: 2 –3 mg administered 3-4 mts before blockade.

  Treatment: IV: 0.1-0.2 mg.

- To prolong the duration of spinal anesthesia:

Addition of 2 – 5mg to local anesthetic solution, increase the duration of motor block approximately 50% without any increase in the incidence of complication such as nausea, vomiting or blood pressure disturbance.

- Vasoconstrictor for regional analgesia:

Use of 1:2, 00,000 solution of Phenylephrine to the local anesthetic solution can act as local vasoconstrictor for regional analgesia.

REVIEW OF LITERATURE

1**) Dinesh Sahu et al** (2003) [13]

They studied the effects of bolus Ephedrine, Mephentermine, Phenylephrine for the maintenance of arterial pressure during spinal anesthesia for LSCS. Sixty patients in the age group of 20-35 yrs of age with ASA-1, 11 are divided into three groups of 20 each as per the study drugs.

Group P: Phenylephrine 100µg,

Group E: Ephedrine 6 mg,

Group M: Mephentermine 6 mg.

In this study all the three vasopressor effectively maintained arterial pressure within 20% of baseline value though Phenylephrine maintained better in first 6minutes of bolus dose as compared with Ephedrine and Mephentermine. Phenylephrine causes significant reduction in heart rate after the bolus dose. They concluded that all the three vasopressor are effective in IV bolus form in maintenance of arterial pressure within 20% limit of baseline though Phenylephrine has quicker peak effect and it causes reduction in heart rate which may be advantageous in cardiac patients and patients in whom tachycardia is Undesirable.

2) **Moran DH et al** (1991) [14]

They compared Ephedrine and Phenylephrine in the prevention of maternal hypotension following spinal anesthesia for caesarean section. Patients were randomly assigned to receive either Ephedrine in 10 mg IV bolus injections or Phenylephrine in 80 µg IV bolus injections to maintain

systolic BP above 100 mmHg. Maternal venous, umbilical artery, and umbilical vein blood gases were measured, and neonatal APGAR scores and early neonatal neurobehavioral scale scores were assessed.

There were significant differences between the groups in mean umbilical artery pH, PCO_2 and base deficit, although all values obtained were within normal limits. There were no significant differences between the groups in the remaining acid-base values, neonatal APGAR scores and early neonatal neurobehavioral scale scores, or frequency of maternal nausea and vomiting. Finally they concluded that Phenylephrine is as effective as Ephedrine in the treatment of maternal hypotension, and when used in small increments, it appears to have no adverse neonatal effects in healthy non-laboring parturients.

3) **Laporta et al** (1995) [15]

They compared maternal and neonatal catecholamine concentrations, following the use of either Phenylephrine or Ephedrine to treat a drop in maternal blood pressure after spinal anesthesia for caesarean section. Patients were randomly assigned to one of two groups. For decrease in maternal BP

Group 1: Received Ephedrine 5 mg IV bolus.

Group 2: Received Phenylephrine 40 μg IV bolus.

Maternal vein, umbilical vein and Umbilical artery were taken at the time of delivery and analyzed for catecholamine concentrations and blood gas values. They found that Phenylephrine appears to be safe and effective as Ephedrine in treatment of drop in blood pressure in healthy non-laboring parturient undergoing LSCS. The use of Phenylephrine was associated with neither significantly lower concentrations of nor adrenaline in both mother and neonate.

4) **Anna Lee et al** (2002) [16]

In their quantitative systematic review, they compared the efficacy and safety of Ephedrine with Phenylephrine for the prevention and treatment of hypotension during spinal anesthesia for cesarean delivery. Seven randomized controlled trials were identified after a systematic search of electronic databases, published articles, and contact with authors. Outcomes assessed were maternal hypotension, hypertension and bradycardia, and neonatal umbilical cord blood pH values and APGAR scores. For the management (prevention and treatment) of hypotension, there was no difference between Phenylephrine and Ephedrine. Maternal bradycardia was more likely to occur with Phenylephrine than with Ephedrine. There was no difference between the two vasopressors in the incidence of true fetal acidosis or Apgar score of <7 at 1 and 5 min.

This systematic review does not support the traditional idea that Ephedrine is the preferred choice for the management of maternal hypotension during spinal anaesthesia for cesarean delivery in healthy non laboring parturients.

5) **Thomas DG et al** (1996) [17].

In their study they compared the efficacy of bolus Ephedrine and Phenylephrine for maintenance of arterial pressure during spinal anaesthesia for caesarean section. They studied 38 healthy women undergoing elective LSCS under spinal anaesthesia and were allocated randomly to receive boluses of either Phenylephrine 100 µg or Ephedrine 5 mg for the

maintenance of maternal arterial pressure. Maternal arterial pressure (BP) and heart rate were measured every minute.

They concluded that in both groups median (range) number of boluses of Ephedrine and Phenylephrine was similar. Maternal systolic BP and cardiac output changes are similar in both groups, but the mean maximum percentage change in maternal HR was larger in Phenylephrine group than in the ephedrine group. As a consequence atropine was required in 11/18 women in the Phenylephrine group compared with 2/19 in the Ephedrine group. Also no neonate had an Apgar of less than 7 at any point of study. They finally concluded the use of Phenylephrine for the maintenance of maternal arterial pressure during spinal anesthesia for LSCS.

6) **Ngan Kee et al** (2006) [18]

Historically, Ephedrine has been recommended as the best vasopressor in Obstetrics because animal studies showed it causes less reduction in uterine blood flow compared with the alpha agonists. Recent clinical evidence, however, suggest that this is not as initially thought.

Ephedrine and Phenylephrine have been most investigated. Advantages of ephedrine include familiarity, long history and low propensity for uteroplacental vasoconstriction. Ephedrine, however, is difficult to titrate, causes maternal tachycardia and depresses fetal pH and base excess. Advantages of Phenylephrine include high efficacy, ease of titration and the ability to use liberal doses to maintain maternal blood pressure near normal and prevent nausea and vomiting without causing fetal acidosis. Phenylephrine, however, may decrease maternal heart rate and cardiac output and few data are available on its use in high risk cases.

They finally concluded based on their observations, that, Phenylephrine is the vasopressor that closely meets the criteria for the best vasopressor in Obstetrics.

7) **Cyna AM et al** (2006) [19]

They studied the randomized controlled trials comparing the interventions to prevent hypotension with placebo or alternative treatment in women having spinal anaesthesia for cesarean section. They included 75 trials in their study from Cochrane pregnancy and childbirth group's trial register.

They found that Ephedrine was significantly more effective than control or crystalloid in preventing hypotension. No significant differences in hypotension were seen between Ephedrine and Phenylephrine. Phenylephrine was more effective than controls. High rates or doses of Ephedrine may increase the incidence of hypertension and tachycardia.

They finally concluded that interventions like colloids, Ephedrine, Phenylephrine or lower leg compression can reduce the incidence of hypotension; none have been shown to eliminate the need to treat maternal hypotension during spinal anesthesia for cesarean delivery.

8) **Ram Nathan et al** (1988) [20]

Maternal homodynamic changes and neonatal acid-base status were assessed in 127 healthy patients undergoing elective cesarean under epidural anesthesia in their study. An impedance cardiograph was used to measure stroke volume, ejection fraction and end diastolic volume. In addition neonatal umbilical venous and arterial PO_2, PCO_2,pH, base excess, lactate, pyruvate, excess lactate, and L/P ratio were measured at birth. Patients were divided into three groups.

Group 1: Required no vasopressor (normotensive controls)

Group 2: Mean blood pressure decreased from 90 mm Hg.

Group 3: Mean blood pressure decreased from 83 to 62 mm Hg.

Phenylephrine was administered in 100 micrograms increments to maintain systolic BP greater than 100 mm Hg. They concluded that

- Transient maternal hypotension does not affect neonatal acid base status.
- Both Ephedrine and Phenylephrine increase cardiac preload.
- An alpha agent like Phenylephrine does not cause fetal acidosis when used for treating maternal hypotension.

9) **David Cooper et al** (2002) [21]

They compared Phenylephrine 100 µg, Ephedrine 3mg/ml and Phenylephrine 50 µg/ml & Ephedrine 1.5mg/ml in combination given by infusion to maintain maternal systemic arterial pressure at baseline during spinal anesthesia for LSCS.

They found that fetal acidosis was less frequent in Phenylephrine group and less frequent in combination group than in ephedrine. The mean systolic arterial pressure was similar in three groups. The mean heart rate was higher in Ephedrine group than in the Phenylephrine group or the combination group. Nausea and vomiting was less frequent in Phenylephrine group than in ephedrine group or the combination group. They found that giving Phenylephrine alone by infusion at caesarean delivery was associated with a lower incidence of fetal acidosis and maternal nausea and vomiting than giving Ephedrine alone. There was no advantage in combining both drugs because it increased nausea and vomiting and it did not further improve fetal blood gas compared with giving Phenylephrine alone.

They finally concluded that despite the more favorable effects on uterine and placental circulations of Ephedrine over Phenylephrine, no significant differences in fetal acid-base status or lactate concentrations were observed.

10) **Lauckner W et al** (1978) [22]

10 late pregnant women with hypotension were examined before and after the intravenous injection of 30 mg Mephentermine with the method of quantitative sphygmomanometer, the bloodless graphic registration of the arterial blood pressure and direct electronic timing of pulse wave velocity. Systolic and diastolic blood pressure increased significantly. The cause of this rise in arterial blood pressure is the increase in stroke volume exclusively. Heart rate and total peripheral vascular resistance remain constant. This hemodynamic mode of action is a favorable one in regard to protection of uteroplacental blood flow. They finally concluded that Mephentermine is suitable for the treatment of hypotension during pregnancy.

11) **Kansai A et al** (2005) [23]

In their compared the effects of IV infusions of Ephedrine and Mephentermine for maintenance of maternal arterial pressure and neonatal outcome in pregnant women receiving subarachnoid block for LSCS. Sixty patients who developed hypotension following subarachnoid block for LSCS were randomly divided into two groups of 30 each to receive an IV infusions of Ephedrine and Mephentermine. Baseline hemodynamic parameters, hemodynamic changes subsequent to the start of vasopressor infusion, duration of hypotension and amount of vasopressor required were statistically similar in both groups. Neonatal APGAR scores and acid-base profiles were

also comparable. They finally concluded that Mephentermine can be used safely and effectively as Ephedrine for the management of hypotension during spinal anesthesia in patients undergoing elective LSCS.

12) **Casey BM et al** (2001) [24]

The 10 point Apgar score has been used to assess the condition and prognosis of newborn infants throughout the world for almost 50 years. They carried out a retrospective cohort analysis of 151,891 live born singleton infants without malformations who were delivered at 26 weeks of gestation. Paired APGAR scores and umbilical artery blood pH were determined for 145,627 infants to assess which test best predicted neonatal death during the first 28 days after birth.

RESULTS: For 13,399 infants born before term (at 26 to 36 weeks of gestation), the neonatal mortality rate was 315 per 1000 for infants with five minutes Apgar scores of 0 to 3,as compared with 5 per 1000 for infants with five minutes Apgar scores of 7 to 10. For 132,228 infants born at term (37 weeks of gestation or later),the mortality rate was 244 per 1000 for infants with five minute Apgar score of 0 to 3,as compared with 0.2/1000 for infants with 5 minute Apgar scores of 7 to 10. The risk of neonatal death in term infants with five minute Apgar scores of 0 to 3 was eight times the risk in term infants with umbilical artery blood pH values of 7.0 or less.

They finally concluded that Apgar scoring system remains as relevant for the prediction of neonatal survival today as it was almost 50 years ago.

13) **Sergio D. Belzarena, TSA** et al (2006) [25]

This study aimed at comparing ephedrine and etilefrine to correct maternal arterial hypotension during elective Cesarean section under spinal

anesthesia. In this study 120 pregnant patients who were randomly distributed in two equal groups. All patients received spinal anesthesia with bupivacaine, fentanyl and morphine. Noninvasive blood pressure and heart rate were monitored. Neonates were evaluated by the Apgar score. The incidence of hypotension, the amount of vasopressor needed to correct it and adverse effects were recorded.

Maternal hypotension was similar in both groups (68%etilefrine group and 63% ephedrine group). The first vasopressor dose was enough to correct hypotension in most patients, with no difference between groups (66% etilefrine, 58% ephedrine). Few patients needed two or more doses to correct hypotension or presented reactive hypertension (24% and 10% in etilefrine and 34% and 8% in ephedrine groups, respectively), without statistically significant differences. There were no differences in adverse effects and neonate tests.

They finally concluded that with the administration method and selected vasopressor doses; there have been no differences between ephedrine and etilefrine used to correct maternal hypotension during Cesarean section under spinal anesthesia.

14) **Ngan Kee et al** (2003) [26]

In this study they have investigated the factors predicting umbilical arterial pH (UA pH) and standard base excess (UA BE) in 337 consecutive elective Caesarean sections performed under spinal anaesthesia. Multiple linear regression analysis was performed with UA pH and UA BE as the dependent factors. They found that the significant factors predicting UA pH were: use of ephedrine, uterine incision-to-delivery time, maximum decrease

in systolic arterial pressure and the interaction between ephedrine use and duration of hypotension.

The significant factors predicting UA BE were: use of ephedrine and the interaction between ephedrine use and duration of hypotension. We conclude that, in order to minimize the risk of foetal acidosis, ephedrine should not be used before delivery, uterine incision-to-delivery time should be as short as possible, and alpha-agonists such as metaraminol or Phenylephrine should be used to minimize both the magnitude and duration of hypotension.

15) Smith N et al **(1972)** [27]

They investigated circulatory effects of single intravenous injections of 0.75 mg/kg Mephentermine in five healthy volunteer subjects. Ninety min after the first injection, atropine 1–2 mg was administered i.v. and the injection of Mephentermine repeated. Cardiac output was measured beat-by-beat with an analogue computer-ballistocardio-graph system, validated by dye-dilution cardiac outputs. The first injection of Mephentermine increased mean arterial pressure, systemic vascular resistance, and left ventricular minute work, with no change in the other variables. The injection of atropine produced a sudden marked increase in heart rate, cardiac output, arterial pressure, and left ventricular work and a fall in stroke volume. The repeat injection of Mephentermine caused considerably smaller changes in the circulation than either previous injection. Atropine thus unmasked the beta-adrenergic stimulating effects of Mephentermine, as well as a surprisingly prolonged action of the agent. It is suggested that the combination of atropine plus Mephentermine be investigated as an approach to improved pressor therapy. Mephentermine is relatively slow in onset, with prolonged peak

effects. For a given increase in arterial pressure, it produces much less drastic changes in other cardiovascular variables than does Methoxamine.

16) **Mercier FJ et al** (2007) [(28))]

They analyzed the different preventive and curative strategies for the management of hypotension during spinal anesthesia for caesarean section. Data related to hypotension during spinal anesthesia for caesarean section were searched in the Medline database.

Hypotension during caesarean section under spinal anesthesia is very frequent (55 to 90%) if not prevented. Crystalloid preload alone is ineffective. Colloid preload is effective but might be better used as a second line treatment. Ephedrine has been the vasopressor of choice for long, but has a weak prophylactic efficacy. In addition, it can induce maternal cardiovascular adverse effects and fetal acidosis. Prophylactic Phenylephrine, with or without ephedrine according to maternal heart rate, is at least as effective as ephedrine, with less adverse effects.

They finally concluded that Hypotension during spinal anesthesia for caesarean section must be systematically detected, prevented and treated without delay. The association of vasopressor(s) (Phenylephrine with or without ephedrine) with a rapid crystalloid loading at the time of spinal injection represents the most interesting strategy nowadays.

17) **Emmett RS et al** (2001) [(29)]

In this review they assessed the relative efficacy and side effects of prophylactic interventions for hypotension following spinal anaesthesia for caesarean section. Twenty-five trials (1477 women) meet their inclusion criteria. From the data collected they concluded that Ephedrine is associated

with dose-related maternal hypertension and tachycardia, and fetal acidosis of uncertain clinical significance. They concluded that no intervention reliably prevents hypotension during spinal anesthesia for caesarean section

18) **Ayorinde BT** et al (2001) [30]

They evaluated pre-emptive intramuscular in 108 patients undergoing elective Caesarean section under spinal anesthesia, assigned to four groups in a randomized, double-blind, placebo-controlled study. Group 1 received pre-emptive Phenylephrine 4 mg i.m., group 2 received Phenylephrine 2 mg i.m., group 3 received ephedrine 45 mg i.m., while controls received an i.m. injection of saline, all given immediately after induction of spinal anesthesia.

Hypotension was defined as a 25% decrease in mean arterial pressure (MAP). Rescue intravenous (i.v.) boluses of ephedrine were given if the patient was hypotensive or reported nausea, vomiting or dizziness. The incidence of hypotension was 33% in the Phenylephrine 4 mg group compared with 70% in the control and Phenylephrine 2 mg groups, and 48% in the ephedrine 45 mg group. The Phenylephrine 4 mg and ephedrine 45 mg groups had a significantly lower percentage reduction in MAP compared with controls. They also had a lower total dose of rescue i.v. ephedrine compared with controls. Neonatal Apgar scores and umbilical artery pH were comparable in all the three groups. They conclude that pre-emptive i.m. Phenylephrine 4 mg and ephedrine 45 mg reduce the severity of hypotension and the total dose of rescue i.v. ephedrine during spinal anesthesia for Caesarean section.

19**) Ngan Kee WD** et al (2004) [31]

In this randomized, double blinded, controlled trial, they investigated the prophylactic infusion of IV Phenylephrine for the prevention of hypotension during spinal anaesthesia for cesarean delivery.

Study group: After SAB, Phenylephrine was infused at 100µg/min for 3 mts. Then Phenylephrine was infused at 100µg/min whenever systolic BP was less than baseline value. Control group: After SAB, Phenylephrine was given as 100µg IV bolus whenever systolic BP falls below the base line value. Phenylephrine infusion decreased the incidence (23% versus 88%), frequency, and magnitude (median minimum SAP, 106 mmHg; range 95-111 mmHg; versus median, 80 mmHg; range, 73-93 mmHg) of hypotension of control. Heart rate was significantly slower over time in the infusion group compared with the control group. In both groups umbilical cord blood gases and Apgar scores were similar. They finally concluded that in patients receiving spinal anaesthesia for cesarean delivery, a prophylactic infusion of Phenylephrine 100µg/min, decreased the incidence, frequency, and magnitude of hypotension with equivalent neonatal outcome compared with a control group receiving IV bolus Phenylephrine.

20) **Warwick D** et al (2007) [32]

In this review they discussed about various measures to prevent and treat hypotension. In contrast to early reports, recent studies have not shown intravenous crystalloid prehydration to be very effective. Colloids are more effective but are expensive and have potential adverse effects. Rapid infusion of intravenous crystalloid after induction (co hydration) appears more effective than prehydration. Although historical studies supported use of ephedrine because of its low propensity to reduce uteroplacental blood flow, recent studies support use of α-agonists such as Phenylephrine. Phenylephrine

is more effective and can be titrated more easily than ephedrine, and it has a less depressive effect on fetal pH and base excess. It may be given as boluses (50–100 μg) or by infusion (50–100 μg/min). A Phenylephrine infusion combined with co hydration is effective for preventing hypotension in most patients. Current evidence suggests that infusions are best titrated to maintain maternal blood pressure near to baseline values.

21) **Afshari A** et al (2006) [33]

Spinal anesthesia for caesarean delivery may be associated with hypotension and fetal acidosis. Prophylactic infusion of Phenylephrine (PE) immediately after the induction of anaesthesia appears to be a more effective approach than administration of ephedrine to reduce the incidence, frequency and severity of hypotension. Furthermore, PE appears to be associated with better fetal acid-base status than is ephedrine.

22) **Critchley LAH** et al (1995) [34]

They compared the hemodynamic effects of ephedrine alone with ephedrine and colloid for the treatment of hypotension produced by sub arachnoid anaesthesia in 30 patients aged 60–90 yr with fractures of the neck of femur.

Group one received ephedrine as an initial bolus dose of 0.2 mg kg^{-1} followed by an infusion of 0.5 mg kg^{-1} h^{-1}. Group two received ephedrine and colloid 8 ml kg^{-1}. If necessary, up to three rescue bolus doses of ephedrine (0.1 mg kg^{-1} and then colloid solution (8 ml kg^{-1} were given to maintain systolic arterial pressure (SAP) at > 75% of baseline. Arterial pressures, central venous pressure (CVP), cardiac index (CI), stroke index (SI) and heart rate (HR) were measured. In patients receiving ephedrine only, SVRI, CVP

and SI decreased and HR increased. Five patients in this group required colloid, the effect of which was to restore CVP, increase CI and SI, and decrease HR. In patients receiving ephedrine and colloid solution, SVRI decreased and CI, SI and HR increased. Ephedrine was not a potent arterial vasoconstrictor and SAP was maintained mainly by increases in SI and HR.

23**) Brooker RF** et al (1997) [35]

Using a prospective, double-blind, randomized, cross-over study design, 13 patients received sequential infusions of epinephrine and Phenylephrine to manage hypotension after hyperbaric tetracaine (10 mg) spinal anaesthesia. Blood pressure, heart rate, and stroke volume were recorded at baseline, 5 min after injection of tetracaine, and before and after management of hypotension with epinephrine and Phenylephrine. Five min after placement of a hyperbaric tetracaine spinal anaesthesia, significant decrease in systolic, diastolic, and mean arterial pressures occurred. Phenylephrine was effective at restoring systolic blood pressure after spinal anesthesia but was associated with a decrease in heart rate and in cardiac output. They finally concluded that Phenylephrine management of tetracaine spinal-induced hypotension decreases heart rate and cardiac output while restoring systolic, mean, and diastolic blood pressure.

24) **Critchley LA** et al (1994) [36]

In this study they compared three methods of preventing hypotension during subarachnoid anesthesia. They attempted to maintain systolic arterial pressure (SAP) greater than 75% of baseline by use of i.v. fluids (preloading with normal saline 16 ml kg-1 and, if necessary, three subsequent boluses of 2.5 ml kg-1), an infusion of metaraminol titrated as necessary between 0 and

5 mg h-1 and an infusion of ephedrine titrated as necessary between 0 and 120 mg h-1. SAP and mean arterial pressure (MAP), central venous pressure (CVP) cardiac index (CI), stroke index (SI) and heart rate (HR). Ephedrine failed to maintain SAP in two of 12 patients and was accompanied by several cardiovascular changes: HR (12%) increased and SI, CVP and SVRI decreased. Treatment failures resulted from failures to maintain SVRI in the fluid group and CVP and SVRI in the ephedrine group.

25) **Yap JC** et al (1998) [37]

They aimed to compare the efficacy of fluid preloading with two recently recommended fluid-vasopressor regimens for maintaining blood pressure during subarachnoid anaesthesia in the elderly. Sixty elderly patients requiring surgery for traumatic hip fractures received subarachnoid anaesthesia using 0.05 ml/kg of 0.5% heavy bupivacaine.

Hypotension, i.e. systolic arterial pressure < 75% of baseline, was prevented or treated by: A--normal saline 16 ml/kg plus intravenous ephedrine boluses (0.1 mg/kg); B--normal saline 8 ml/kg plus intramuscular depot ephedrine (0.5 mg/kg); or C--Haemaccel 8 ml/kg plus metaraminol infusion. Systolic arterial pressure and heart rate were recorded. Systolic arterial pressure decreased in all groups after five minutes. Decreases were greatest in group A. Heart rate increased by 7% group A and decreased by 9% in group C. During the first hour, hypotension was present for 47%, 25% and 20% of the time in groups A, B and C respectively and overcorrection of systolic arterial pressure occurred in 19% of the time in group C. they concluded that treatment A was inadequate in preventing hypotension. Treatments B and C were more effective but were associated with an

increased heart rate and overcorrection of systolic arterial pressure respectively.

26) **Turkoz A** et al (2002) [38]

Maternal cardiovascular changes and neonatal acid-base status, including lactate levels, were assessed in 30 healthy women undergoing elective caesarean section under spinal anaesthesia. Patients were allocated randomly to receive IV ephedrine infusion (5 mg/mt immediately after the spinal injection or bolus administration of IV ephedrine (10 mg) in case of development of hypotension. Maternal and neonatal blood pressure, heart rate and acid-base status including lactate levels were compared between the groups. Systolic blood pressure in the bolus group was significantly lower when compared to the infusion group. Nausea was observed in one patient (6%) in the infusion group and nausea and vomiting were observed in 10 patients (66%) in the bolus group. In conclusion, ephedrine infusion prevented maternal hypotension, reduced the incidence of nausea and vomiting and led to improved umbilical blood pH during spinal anaesthesia for caesarean section.

27) **Hall PA** et al (1994) [39]

Maternal cardiovascular changes and neonatal acid base status were assessed in 29 healthy women undergoing elective LSCS under spinal anaesthesia. The patients were allocated randomly to one three groups to receive an IV infusion of one of the following. Ephedrine 1mg/mt (E1), ephedrine 2mg/mt (E2) or Phenylephrine 10µg/mt (P). Invasive arterial BP was monitored continuously and whenever hypotension occurs Ephedrine 6mg IV bolus was given in groups E1&E2 and Phenylephrine 20µg in group

P. They found that Phenylephrine was shown to be significantly less effective in maintaining systolic BP within 20% of baseline on comparing with Ephedrine when administered at this dosage. Neonatal Apgar scores and acid-base profiles were comparable in all the three groups

28) **Alahutta S** et al (1992) [40]

In this study patients were randomized into two groups, to be given either Ephedrine or Phenylephrine as a prophylactic infusion supplemented with minor boluses to maintain the systolic arterial pressure 20% above the baseline values during spinal anaesthesia for cesarean section. They found that both the vasopressors restored maternal arterial pressure effectively. Changes in uterine blood flow occurred during Phenylephrine infusion and not during Ephedrine infusion. But the Apgar scores and acid-base values in the umbilical cord were within the normal range in both groups.

MATERIALS AND METHODS

This study was conducted at **INSTITUTE FOR SOCIAL OBSTETRICS**, **GOVERNMENT KASTURBA GANDHI HOSPITAL**, Triplicane, attached to **MADRAS MEDICAL COLLEGE**, Chennai-600005 between June 2007 to July 2007 on 90 patients undergoing elective and emergency LSCS. The study was done after getting institutional approval. Written informed consent was obtained from all the patients included in the study.

Study design:

This study was done in a prospective double blind randomized manner. The patients were divided into three groups of 30 each. Patients meeting the criteria were incorporated into the study. Randomization achieved by sealed envelope technique.

Group 1: Patients in this group received Inj Ephedrine 6 mg IV bolus on developing hypotension.

Group 11: Patients in this group received Inj Mephentermine 6 mg IV bolus on developing hypotension.

Group 111: Patients in this group received Inj Phenylephrine 100 microgram IV bolus on developing hypotension.

Selection of cases:

Inclusion criteria:

Patients in age group of 18 – 35 years of age, healthy, ASA I & II patients with singleton full term pregnancy, undergoing elective and emergency LSCS were included in the study.

Exclusion criteria:

1. Patients >35 years of age

2. Known hypertensive patients , patients on anti hypertensive drugs
3. Uncontrolled PIH
4. ASA III , IV patients
5. Multiple Gestation
6. Obese (> 90 kg)
7. Short stature (< 140 cm)

Investigations:

1. Hb%, PCV
2. Blood grouping & typing
3. BT, CT, Platelet count
4. Blood sugar, blood urea, Sr. Creatinine
5. Urine albumin, Sugar

Premedication:

Elective surgery: T. Ranitidine 150 mg PO
T. Metaclopramide 10 mg PO with sips of water 2 hrs before surgery

Emergency surgery: Inj. Ranitidine 50 mg IV
Inj. Metaclopramide 10 mg IV 30 mts before surgery

In the operation theatre appropriate equipment for airway management and emergency drugs were kept ready. Patients were shifted to the operation theatre. The horizontal position of the operating table was checked. The patients were made to lie supine with a pillow under head. The patients were connected to non invasive sphygmomanometer, ECG and pulse oximetry monitor. Intravenous access was obtained with 18 G IV cannula. All patients were preloaded with Ringer lactate (15 ml/Kg) rapidly. The anaesthesiologist unaware of the study drug performed the subarachnoid block and made the observations in all the patients involved in the study.

Patients were placed in right lateral position. Skin over the back was prepared with antiseptic solution and draped with sterile towel. The L3-L4 interspace was identified and 23 G Quicke-Babcock needle was introduced in this space through a midline approach. Once the needle pierced the dura and was in the subarachnoid space, stylet was removed and free flow of CSF was verified and 1.8cc of 0.5% Bupivacaine was administered intrathecally. The patients were turned supine and immediately a wedge was placed under the right flank. Oxygen was administered at a rate of 6 lit/min by a face mask to all the patients.

Inj. Ergometrine 0.25 mg slow IV and Inj. Oxytocin 10 U in 5% Dextrose were given after clamping the cord. Intravenous fluids were administered at a rate of 1000 ml / hr throughout the surgery.

After preloading, Heart rate, Systolic BP, Diastolic BP, MAP and SPO2 were recorded and taken as baseline value. The same parameters were monitored every minute till the onset of hypotension and then recorded for every two minutes for ten minutes and thereafter every 5 minutes till the end of surgery.

Whenever Hypotension (Fall in Systolic BP < 20 % from baseline value or systolic BP < 90 mm Hg) occurred, the study drug was given IV bolus. The time of onset of hypotension after SAB, lowest systolic BP recorded, total no. boluses and total mg of vasopressor used were recorded. The time of onset of bradycardia (HR < 60 / min) was noted and was treated with Inj. Atropine 0.3 mg IV bolus.

The highest level of sensory block was assessed by pinprick method 5 min after SAB. The subarachnoid block-delivery interval was recorded. Neonatal outcome was assessed by the pediatrician by APGAR score at first and fifth min.

The incidence of tachycardia (HR > 150 / min) and its time of onset was noted. The occurrence of hypertension (> 20 % increase in systolic BP from baseline values) was noted. The incidence of nausea and vomiting & its time of onset were also noted. Total intravenous fluids given and urine output was also noted.

Study material:

A total of 30 cases each were randomly allocated to one of the following three groups of study:

GROUP I : Received Inj Ephedrine 6mg IV bolus

GROUP II : Received Inj Mephentermine 6mg IV bolus

GROUP III : Received Inj Phenylephrine 100µg IV bolus

Statistical method:

The descriptive statistics of the variables studied were represented as two-way tables. The categorical factors were represented by the number and frequency (%) of cases. The continuous variables were represented by measures of central frequency (like mean, median & mode) and deviation (say, standard deviation and range). The differences in the proportions of are tested for statistical significance using non-parametric Chi-square test for variables measured on nominal scale. When testing for two factors, the Mann-Whitney “U” test or Wilcoxon two sample test (by Kruskal-Wallis “H” test which is equivalent to chi-square) was used. Fisher’s exact probability test was used wherever indicated. For variables measured on a continuous scale, one-way analysis of variance (ANOVA) was employed to elicit the statistical significance of variation when three variables were taken together. When testing for two groups (pair wise), Student “t” test is used to test for statistical significance in the differences of the two means.

OBSERVATION AND RESULTS

Demographic Data:

All the three groups were comparable with respect to their age, height, weight, baseline systolic BP, diastolic BP, MAP, heart rate. Also the time to develop hypotension, lowest systolic BP recorded, SAB-delivery time were comparable in the three groups and was not statistically significant. The level of sensory blockade was comparable in all the three groups and was not statistically significant.

There was no statistically significant difference among the three groups in demographic aspect.

Table 1: Distribution of age of cases by groups[$]

Age	Group I	Group II	Group III	p-value
No. of cases	30	30	30	
Mean	25.0	24.6	24.1	
S.D.	2.91	3.63	2.89	0.52
Median	24.5	24	24	
Range	21 – 31	18 – 32	19 – 32	
Stat	p-value			
Significance	0.22			
Gr I vs Gr III	0.58			
Gr II vs Gr III	0.58			
Gr I vs Gr II				

[$] Not statistically significant

The variation in the mean distribution of cases by age between Group I, Group II and Group III was not statistically significant (p=0.52). The same was observed between pairs of groups studied.

Table 2: Distribution of height of cases by groups[$]

Height	Group I	Group II	Group III	p-value
No. of cases	30	30	30	
Mean	156.8	156.0	154.6	
S.D.	5.73	5.52	6.39	0.36
Median	158	156	154	
Range	145 – 168	145 – 165	144 – 165	
Stat. Significance	p-value			
Gr. I vs. Gr. III	0.17			
Gr. II vs. Gr. III	0.38			
Gr. I vs. Gr. II	0.58			

[$] Not statistically significant

The variation in the mean values by height between Group I, Group II and Group III was not statistically significant. The same results were forthcoming for pair wise comparison between groups.

Table 3: Distribution of weight of cases by groups[$]

Weight	Group I	Group II	Group III	p-value
No. of cases	30	30	30	
Mean	61.8	61.1	61.7	
S.D.	5.17	5.66	5.25	0.35
Median	62	60	62	
Range	52 – 72	49 – 72	52 – 74	
Stat. Significance	p-value			
Gr. I vs. Gr. III	0.74			
Gr. II vs. Gr. III	0.15			
Gr. I vs. Gr. II	0.44			

[$] Not statistically significant

The variation in the mean values by weight between Group I, Group II and Group III was not statistically significant. The same results were forthcoming for pair wise comparison between groups.

Table 4: Distribution of cases by groups and sensory block[$]

Sensory block	Group I		Group II		Group III		p-value
	No.	%	No.	%	No.	%	
T4 T5 T6	21 7 2	70. 0 23. 3 6.7	20 5 5	66. 6 16. 7 16. 7	20 9 1	66. 6 30. 0 3.4	0.35
Stat. Significance	p-value						
Gr. I vs. Gr. III	0.74						
Gr. II vs Gr. III	0.15						
Gr. I vs Gr. II	0.44						

[$] Not statistically significant

The distribution of cases by sensory block grade and groups was not statistically significant. Pair wise comparisons of groups also revealed similar results.

Table 5: Distribution of Time to develop hypotension by groups[$]

Time in sec	Group. I		Group II		Group III		p-value
	No.	%	No.	%	No.	%	
1	1	3.3	1	3.3	0	0.0	
2	16	53.3	21	70.0	15	50.0	
4	7	23.3	8	26.7	13	43.3	0.16
6	5	16.8	0	0.0	2	6.7	
8	1	3.3	0	0.0	0	0.0	
Stat. Significance	p-value						
Gr. I vs. Gr. III	0.28						
Gr. II vs. Gr. III	0.16						
Gr. I vs. Gr. II	0.15						

[$] Not statistically significant

The distribution of time to develop hypotension values between Group I, Group II and Group III did not reveal any statistically significant differences. The results were similar when the groups were compared in pairs.

Table 6: Distribution of SAB-Delivery time by groups[$]

SAB-Delivery time in mts	Group. I		Group II		Group III		p-value
	No.	%	No.	%	No.	%	
4	2	6.7	1	3.3	0	0.0	
5	1	3.3	2	6.7	1	3.3	
6	6	20.0	10	33.3	9	30.0	
7	5	16.7	4	13.3	8	26.7	0.53
8	6	20.0	5	16.7	4	13.3	
9	9	30.0	8	26.7	4	13.3	
10	1	3.3	0	0.0	3	10.0	
11	0	0.0	0	0.0	1	3.3	

Stat. Significance	p-value
Gr. I vs. Control	0.38
Gr. II vs. Control	0.32
Gr. I vs. Gr. II	0.82

[$] Not statistically significant

The distribution of SAB-Delivery values between Group I, Group II and Group III did not reveal any statistically significant differences. The results were similar when the groups were compared in pairs.

Table 7: Distribution of Lowest Systolic BP values by groups[$]

Low systolic BP	Group. I	Group II	Group III	p-value
Number of cases	30	30	30	
Mean	85.0	82.7	85.3	
S.D.	5.03	6.02	4.60	0.12
Median	86	84	87.5	
Range	75 – 93	71 – 90	73 – 90	
Stat. Significance	p-value			
Gr. I vs. Control	0.77			
Gr. II vs. Control	0.07			
Gr. I vs. Gr. II	0.12			

[$] Not statistically significant

The comparison of mean lowest systolic BP values between the three groups was not statistically significant. The results were the same for pair wise comparisons of groups.

Table 8: Mean Distribution of cases by groups and baseline HR SBP, DBP, MAP[$]

At Baseline	Group I (n=30)	Group II (n=30)	Group III (n=30)	p-value
Heart rate				
Mean	86.4	83.9	90.1	0.14
SD	12.25	10.39	13.62	
Systolic BP				
Mean	119.6	119.2	119.5	0.98
SD	7.68	8.46	8.45	

Diastolic BP Mean SD	74.0 6.38	78.8 7.58	76.7 7.43	0.07
MAP value Mean SD	89.2 5.57	92.3 7.11	90.3 6.93	0.19

[$] Not statistically significant

The mean distribution of anthropometric values of the heart rate, systolic BP and MAP at baseline between the three groups was not statistically significant. . The results were the same for pair wise comparisons of groups.

Haemodynamic variables:

Table 9: Mean Distribution of cases by groups and HR

HR	**Group I** (n=30)	**Group II** (n=30)	**Group III** (n=30)	**p-value**
Base line Mean SD	86.4 12.25	83.9 10.39	90.1 13.62	0.14
HP(VP given) Mean SD	90.7 25.52	90.9 18.47	87.6 17.93	0.24
2 mts after VP Mean SD	93.1 21.21	93.8 18.3	83.2 17.8	0.04*
4-mts Mean SD	93.7 19.49	93.8 20.50	91.3 12.64	0.83
6-mts Mean	96.2	99.0	94.6	0.58

SD	17.58	18.16	13.10	
8-mts				
Mean	96.5	98.6	94.0	0.51
SD	17.24	15.31	12.76	
10-mts				
Mean	97.2	97.2	92.7	0.40
SD	15.36	15.51	13.07	
15-mts				
Mean	96.6	96.1	92.1	0.43
SD	16.31	15.42	12.53	
20-mts				
Mean	95.6	96.7	93.8	0.74
SD	15.96	15.88	12.17	
25-mts	N=29	N=30	N=30	
Mean	96.3	95.8	93.1	0.63
SD	15.31	14.41	11.98	
30-mts	N=28	N=30	N=29	
Mean	95.5	96.1	91.9	0.42
SD	12.38	14.67	11.94	

*statistically significant

The mean value of heart rate was generally the highest in Group II followed by Group I and Group III. The mean variation of heart rate values between the three groups was statistically significant at 2mts. Pair wise comparison of groups showed that the differences in mean values were statistically significant between Group II and III and between Group I and III at 2-mts.

Table 10: Mean Distribution of cases by groups and Systolic BP[$]

SYSTOLIC BP	Group I (n=30)	Group II (n=30)	Group III (n=30)	p-value
Base line				
Mean	119.6	119.2	119.5	0.98
SD	7.68	8.46	8.45	
HP(VP given)				
Mean	85.3	82.7	85.7	0.07
SD	5.08	6.11	5.21	
2 mts after VP				
Mean	104.6	105.5	111.9	0.10
SD	16.99	12.20	12.64	
4-mts				
Mean	114.2	108.7	112.7	0.26
SD	16.04	10.69	13.25	
6-mts				
Mean	112.6	112.2	113.9	0.81
SD	12.33	11.11	9.16	
8-mts				
Mean	110.9	112.6	114.3	0.45
SD	8.79	10.55	11.76	
10-mts				
Mean	112.0	113.5	114.6	0.63
SD	10.02	10.39	11.00	
15-mts				
Mean	111.5	111.5	114.7	0.37
SD	9.25	10.64	9.96	
20-mts				
Mean	111.8	112.7	115.1	0.35
SD	7.05	9.83	9.91	
25-mts	N=29	N=30	N=30	
Mean	110.0	110.1	114.7	0.38
SD	9.02	21.82	10.57	
30-mts	N=28	N=30	N=29	
Mean	114.9	115.2	116.0	0.90
SD	7.80	11.44	9.53	

[$] Not statistically significant

The distribution of mean values of systolic BP was generally the highest in Group III especially after 6 mts. The variation in mean systolic values between the three groups was not statistically significant at any time point studied.

Table 11: Mean Distribution of cases by groups and Diastolic BP

DIASTOLIC BP	Group I (n=30)	Group II (n=30)	Group III (n=30)	p-value
Base line				
Mean	74.0	78.8	76.7	0.07
SD	6.38	7.58	7.43	
HP(VP given)				
Mean	50.6	51.8	49.3	0.62
SD	9.95	9.22	9.82	
2 mts after VP				
Mean	59.6	66.0	69.0	0.01*
SD	12.56	11.83	12.03	
4-mts				
Mean	64.6	66.4	68.0	0.54
SD	13.79	8.63	14.29	
6-mts				
Mean	64.5	68.6	66.2	0.39
SD	10.33	10.10	13.62	
8-mts				
Mean	64.8	70.2	66.5	0.15
SD	9.32	8.03	13.73	
10-mts				
Mean	65.8	70.5	69.0	0.19
SD	9.03	9.66	11.2	
15-mts				
Mean	65.4	69.8	68.5	0.20
SD	9.54	9.50	9.94	
20-mts				
Mean	64.9	70.5	69.7	0.03*
SD	8.15	7.97	9.65	
25-mts	N=29	N=30	N=30	
Mean	64.4	72.2	68.5	0.009*
SD	8.65	10.39	9.22	
30-mts	N=28	N=30	N=29	
Mean	65.3	71.8	71.9	0.01*
SD	9.45	9.93	8.97	

* Statistically significant

The mean value of diastolic BP was greater in Group III than Group I or Group II values at 2nd and 4th mt. The variation in the mean values of diastolic BP between the three groups was statistically significant at 2-mts (p=0.01) and between 20 and 30 minutes. Pair wise comparison of groups

revealed that the mean differences were statistically significant between Group I and Group II at 8-mts (p=0.02).

Table 12: Mean Distribution of cases by groups and MAP

MAP	Group I (n=30)	Group II (n=30)	Group III (n=30)	p-value
Base line				
Mean	89.2	92.3	90.3	0.19
SD	5.57	7.11	6.93	
HP(VP given)				
Mean	62.2	62.1	61.4	0.89
SD	7.69	7.47	7.33	
2 mts after VP				
Mean	74.6	83.7	83.3	0.003*
SD	13.38	7.60	11.7	
4-mts				
Mean	81.0	71.8	82.8	<0.001*
SD	13.28	5.95	13.31	
6-mts				
Mean	80.6	80.9	82.1	0.83
SD	10.11	8.47	10.74	
8-mts				
Mean	80.2	83.1	82.5	0.46
SD	8.11	6.79	12.50	
10-mts				
Mean	81.2	84.4	84.2	0.35
SD	8.43	9.46	10.11	
15-mts				
Mean	80.8	84.2	83.9	0.26
SD	8.42	9.09	9.00	
20-mts				
Mean	80.5	84.8	84.9	0.054
SD	6.82	8.13	9.07	
25-mts	N=29	N=30	N=30	
Mean	79.6	85.3	83.9	0.04*
SD	7.68	9.65	8.66	
30-mts	N=28	N=30	N=29	
Mean	82.0	85.4	86.6	0.10
SD	7.03	9.16	8.40	

* Statistically significant

The mean differences in MAP values between the three groups were statistically significant at 2-mts (p=0.003), 4 mts (p<0.001) and 25-mts

(p=0.04). The pair wise comparisons between Group I and Group II was statistically significant at 25-mts (p=0.02) and between Group I and Group III at 30-mts (p=0.03).

Table 13: Distribution of Bolus dose required by groups

Bolus dose	Group I		Group II		Group III		p-value
	No.	%	No.	%	No.	%	
One	21	70.0	23	76.7	27	90.0	0.23
Two	8	26.7	7	23.3	3	10.0	
Three	1	3.3	0	0.0	0	0.0	

In Group-1: 70% of patients required one, 27% of patients required two and 3% of patients required three bolus doses to maintain systolic pressure within 20%limit of basal value.

In Group-11: 77% of patients required one and 23% of patients required two bolus doses to maintain systolic pressure within 20%limit of basal value.

In Group-111: 90% of patients required one and 10% of patients required two doses to maintain systolic pressure within 20%limit of basal value.

Side effects:

Table 14: Distribution of cases by groups and co-morbid conditions[$]

Co-morbid conditions	Group I		Group II		Group III	
	No.	%	No.	%	No.	%
Brachycardia						
Yes	5	16.7	3	10.0	7	23.3
No	25	83.3	27	90.0	23	76.7
Tachycardia						
Yes	1	3.3	1	3.3	0	0.0
No	29	96.7	29	96.7	30	100.0
Hypertension						
Yes	2	6.7	0	0.0	0	0.0
No	28	93.3	30	100.0	30	100.0

Bradycardia: 17% of patients in group-1, 10% of patients in group-11 and 24% of patients in group-111 developed bradycardia and was subsequently treated with Inj.Atropine 0.6mg IV bolus.

Tachycardia: 4% of patients in group-1&11 developed tachycardia.

Hypertension: 7% of patients in group-1 developed hypertension.

Table 15: Distribution of cases by groups and conditions

Conditions	Group I		Group II		Group III	
	No.	%	No.	%	No.	%
Nausea &Vomiting						
Yes	5	16.7	6	20.0	3	10.0
No	25	83.3	24	80.0	27	90.0

5% in group-1, 6% in group-11, 3% in group-111 developed nausea and vomiting.

Neonatal outcome:

Table 16: Distribution of APGAR-1 by groups[$]

APGAR-1	Group. I		Group II		Group III		p-value
	No.	%	No.	%	No.	%	
6 7	2 28	6.7 93.3	2 28	6.7 93.3	1 29	3.3 96.7	0.81
Stat. Significance	p-value						
Gr. I vs. Gr. III	1.00						
Gr. II vs. Gr. III	1.00						
Gr. I vs. Gr. II	1.00						

[$] Not statistically significant

Table 17: Distribution of APGAR-5 by groups[$]

APGAR-5	Group. I		Group II		Group III		p-value
	No.	%	No.	%	No.	%	
7 8	2 28	6.7 93.3	1 29	3.3 96.7	1 29	3.3 96.7	0.77
Stat. Significance	p-value						
Gr. I vs. Gr. III	1.00						
Gr. II vs. Gr. III	1.00						
Gr. I vs. Gr. II	1.00						

[$] Not statistically significant

The distribution of APGAR scores at 1 and 5 minutes between the three groups was not statistically significant. The pair wise comparisons too revealed similar results. At 5 mt no neonate had an Apgar score of less than 7.

DISCUSSION

After subarachnoid block for caesarean section, hypotension can be minimized by the use of IV fluid preload, avoidance of aortocaval compression and judicious use of vasopressor agent. It has been shown that the percentage decrease in placental perfusion is related to the percentage reduction in maternal arterial pressure and not to the absolute reduction in pressure [41]. For the purpose of this study, hypotension was defined as a decrease in arterial pressure greater than 20% from baseline systolic pressure.

Ephedrine and Mephentermine have got a mixed action directly as well as indirectly on α and ß receptors, whereas Phenylephrine has pure α receptors activity.

Haemodynamic variables:

Heart rate:

In our study the mean value of heart rate was generally highest in Mephentermine Group followed by Ephedrine and Phenylephrine Groups. Also the mean variation of heart rate between the three groups was statistically significant at 2 mts. Pair wise comparison between the three groups were also statistically significant between the three groups at 2 mts after administration of the vasopressor. In spinal anaesthesia, since there is decreased venous return, decreased venous pressure and a decreased right heart pressure thus slowing of the heart rate is expected on the basis of the Bain bridge reflex. Bradycardia is also expected in high spinal, probably due to some paralysis of the cardio-accelerator nerves. We found that the maternal heart rate was slower with Phenylephrine than with Ephedrine and Mephentermine. This is consistent with the mechanism of action of these drugs that the decrease in heart rate found in Phenylephrine group was due to

pure α receptor activity compared with Ephedrine and Mephentermine as they had got a mixed action directly as well as indirectly on α and ß receptors. Similar results were seen in many studies which was consistent with our study.

In the study done by **Dinesh Sahu** et al [13] Phenylephrine was found to cause significant reduction in heart rate after the bolus dose. In the quantitative systematic review done by **Anna Lee** et al [16] they found that maternal bradycardia was more likely to occur with Phenylephrine than with Ephedrine. Also **Thomas DG** et al [17] on comparing the efficacy of bolus Ephedrine and Phenylephrine, they found that mean maximum percentage change in maternal HR was larger in Phenylephrine group than in the ephedrine group. As a consequence atropine was required in eleven out of eighteen women in the Phenylephrine group compared with two out of eighteen women in the Ephedrine group

In the systematic review by **Ngan Kee** et al [18] he concluded that Phenylephrine may decrease maternal heart rate and cardiac output. In **David Cooper** et al's [21] study on comparing the effects of Ephedrine and Phenylephrine when administered alone and in combinations they found that mean heart rate was higher in Ephedrine group than in the Phenylephrine group or the combination. In the study done by **Lauckner W** et al [22], the efficacy of IV Mephentermine in treating hypotension was studied in 10 late pregnant women undergoing elective LSCS under SAB and they found that heart rate and total peripheral vascular resistance remain constant.

Kansai A et al [23] on comparing the effects of IV infusions of Ephedrine and Mephentermine for maintenance of maternal arterial pressure they found that the baseline haemodynamic parameters, and haemodynamic changes subsequent to the start of vasopressor infusion, were statistically

similar in both groups. In **Ngan Kee WD** et al's [31] study on comparing the effects of prophylactic infusion and bolus Phenylephrine they found that heart rate was significantly slower over time in the infusion group compared with the control group

On comparing the haemodynamic effects of ephedrine alone with ephedrine and colloid for the treatment of hypotension produced by subarachnoid anesthesia in 30 patients aged 60–90 yr with fractures of the neck of femur **Critchley LAH** et al [34] they found that in patients receiving ephedrine only, SVRI, CVP and SI decreased and HR increased and in patients receiving ephedrine and colloid solution, SVRI decreased and CI, SI and HR increased. They finally concluded that Ephedrine was not a potent arterial vasoconstrictor and SAP was maintained mainly by increases in SI and HR.

In the study done by **Brooker RF** et al [35] they found that Phenylephrine was associated with a decrease in heart rate and in cardiac output. In the study done by **Critchley LA** et al [36] Ephedrine was accompanied by increase in HR in 12% of cases. **Yap JC** et al [37] on comparing the efficacy of fluid preloading with IV Ephedrine, IM depot Ephedrine and Metaraminol infusion for maintaining blood pressure they found that heart rate increased by 7% in group receiving IV bolus ephedrine and IM depot Ephedrine was effective but was associated with an increase in heart rate.

Blood pressure:

The systolic, diastolic and mean arterial pressure were decreased statistically significant at the onset of hypotension and increased after the bolus dose of drug in all the three groups. The pressures generally remained high in Mephentermine and Phenylephrine groups when compared with

Ephedrine group. Systolic blood pressure was generally highest in Phenylephrine group immediately after the administration. The diastolic blood pressure was also greater in Phenylephrine group when compared with ephedrine and Mephentermine groups, especially after 2nd and 4th minute, after administration of the drug. In Ephedrine group the diastolic blood pressure was generally less throughout the study period, when compared with other two drugs. MAP was also less in Ephedrine group when compared with Mephentermine and Phenylephrine groups. The mean differences in MAP between the three groups were statistically significant at 2nd, 4th and 25th minute after the administration of vasopressor. This finding is consistent with the onset of action and efficacy of the drug that Phenylephrine has quicker onset of action and better maintenance of arterial pressures when compared with the other two drugs.

Dinesh Sahu et al [13] studied the effects of bolus Ephedrine, Mephentermine, Phenylephrine for the maintenance of arterial pressure during spinal anesthesia for LSCS. In their study all the three vasopressor effectively maintained arterial pressure within 20% of baseline value though Phenylephrine maintained better in first 6minutes of bolus dose as compared with Ephedrine and Mephentermine and Phenylephrine has a quicker peak effect. This finding is consistent with our study.

Laporta et al [15] compared maternal and neonatal catecholamine concentrations, following the use of either bolus Phenylephrine or Ephedrine to treat a drop in maternal blood pressure after spinal anaesthesia for caesarean section. They found that Phenylephrine appears to be safe and effective as Ephedrine in treatment of drop in blood pressure in healthy non-laboring parturient undergoing LSCS

Anna Lee et al [16] in their quantitative systematic review, they found that for the management (prevention and treatment) of hypotension, there was no difference between Phenylephrine and Ephedrine and both effectively maintained the systolic BP within 20% of baseline values. **Thomas DG** et al [17] in their study compared the efficacy of bolus Ephedrine and Phenylephrine for maintenance of arterial pressure during spinal anaesthesia for caesarean section and found that maternal systolic BP and cardiac output changes are similar in both groups

Cyna AM et al [19] studied the randomized controlled trials comparing the interventions to prevent hypotension during spinal anaesthesia for cesarean section. From 75 trials they found that Ephedrine was significantly more effective than control or crystalloid in preventing hypotension. There were no significant differences between Ephedrine and Phenylephrine in treating hypotension. Similar results were obtained from our study also**. Ram Nathan** et al [20] assessed the maternal homodynamic changes and neonatal acid-base status in 127 healthy patients undergoing elective cesarean under epidural anesthesia and concluded that both Ephedrine and Phenylephrine increase cardiac preload and effectively maintained the systolic blood pressure within 20% of baseline values.

David Cooper et al [21] compared Phenylephrine 100 µg, Ephedrine 3mg/ml and Phenylephrine 50 µg/ml & Ephedrine 1.5mg/ml in combination given by infusion to maintain maternal systemic arterial pressure at baseline during spinal anesthesia for LSCS and found that the mean systolic arterial pressure was similar in three groups. **Lauckner W** et al [22] studied the effects of IV Mephentermine in 10 late pregnant women with hypotension after SAB and found that Systolic and diastolic blood pressure increased significantly. The cause of this rise in arterial blood pressure is due to increase in stroke

volume exclusively and no significant changes occurred in heart rate. They finally concluded that Mephentermine is suitable for the treatment of hypotension during pregnancy.

Kansai A et al [23] compared the effects of IV infusions of Ephedrine and Mephentermine for maintenance of maternal arterial pressure receiving subarachnoid block for LSCS and found that baseline hemodynamic parameters, hemodynamic changes subsequent to the start of vasopressor infusion, were statistically similar in both groups. Smith N **et al** [27] investigated circulatory effects of single intravenous injections of 0.75 mg/kg Mephentermine in five healthy volunteer subjects. They found that first injection of Mephentermine increased mean arterial pressure, systemic vascular resistance, and left ventricular minute work, with no change in the other variables.

In the review done by **Warwick D** et al [32] they discussed about various measures to prevent and treat hypotension. Recent studies support use of α-agonists such as Phenylephrine. Phenylephrine is more effective and can be titrated more easily than ephedrine it may be given as boluses (50–100 μg) or by infusion (50–100 μg/min). **Brooker RF** et al [35] studied sequential infusion of Phenylephrine to manage hypotension. In their study also Phenylephrine was effective at restoring systolic blood pressure after spinal anaesthesia. **Yap JC** et al [37] on comparing the efficacy of fluid preloading with two fluid-vasopressor regimens IV ephedrine boluses was more effective in maintaining systolic blood pressure.

Alahutta S et al [40] studied the effects of Ephedrine and Phenylephrine to maintain the systolic arterial pressure 20% above the baseline values during spinal anesthesia for cesarean section. In this study also both the vasopressors restored maternal arterial pressure effectively.

Side effects:

The Heart rate remained generally low in Phenylephrine group when compared with Ephedrine and Mephentermine group. Seven patients developed bradycardia in Phenylephrine group compared with five and three patients in Ephedrine and Mephentermine groups and they were subsequently treated with Inj.Atropine 0.3 mg IV bolus. Out of seven patients who developed bradycardia in Phenylephrine group, five of them developed bradycardia after the administration of the drug. One patient in ephedrine and Mephentermine group developed tachycardia and two patients in ephedrine group developed hypertension. The incidence of tachycardia is more in ephedrine and Mephentermine groups than in Phenylephrine group. This is due to both direct and indirect action of ephedrine and Mephentermine compared with Phenylephrine which has only direct α action. This direct action of Phenylephrine is also responsible for the increased incidence of bradycardia as seen in our study.

In the quantitative systematic review of seven clinical trials, **Anna Lee** et al [16] they found that maternal bradycardia was more likely to occur with Phenylephrine than with Ephedrine. In a review article by **Ngan Kee** et al [18] they found that Ephedrine causes maternal tachycardia when compared with Phenylephrine which causes decrease maternal heart rate**. Cyna** AM et al [19] in their review of 75 clinical trials found that high rates or doses of Ephedrine may increase tachycardia incidence.

David Cooper et al [21] on comparing compared Phenylephrine and Ephedrine they found that the mean heart rate was higher in Ephedrine group than in the Phenylephrine group or the combination group. **Lauckner W** et al [22] found that when Mephentermine was used to treat hypotension during SAB for LSCS, Systolic and diastolic blood pressure increased significantly

with out changes in heart rate. Smith N **et al** [27] investigated circulatory effects of single intravenous injections of 0.75 mg/kg Mephentermine in five healthy volunteer subjects. They found that the first injection of Mephentermine increased mean arterial pressure, systemic vascular resistance, and left ventricular minute work, with no change in the other variables including heart rate. They finally concluded that for a given increase in arterial pressure, it produces much less drastic changes in other cardiovascular variables.

Mercier FJ et al [28] in their review concluded that Ephedrine has been the vasopressor of choice for long, but has a weak prophylactic efficacy and also it can induce maternal cardiovascular adverse effects like tachycardia and hypertension. Also prophylactic Phenylephrine, with or without ephedrine according to maternal heart rate, is at least as effective as ephedrine, with less adverse effects.

Emmett RS et al [29] also on reviewing 27 trials found that Ephedrine is associated with dose-related maternal hypertension and tachycardia. When comparing the hemodynamic effects of ephedrine alone with ephedrine and colloid for the treatment of hypotension **Critchley LAH** et al (1995) [34] found that Ephedrine was not a potent arterial vasoconstrictor and SAP was maintained mainly by increases in stroke index and heart rate.

On comparing three methods (preloading, infusion of ephedrine and Metaraminol) in preventing hypotension during subarachnoid anaesthesia. **Critchley LA** et al [36] found that HR was increased in 12% of patients in patients receiving ephedrine. **Yap JC** et al [37] on comparing the efficacy of fluid preloading with IV Ephedrine, IM Ephedrine and Metaraminol infusion found that Heart rate increased by 7% group receiving IV Ephedrine and also in group receiving intramuscular Ephedrine.

In our study 5% in group-1, 6% in group-11, 3% in group-111 developed nausea and vomiting. There was no significant difference among the three groups in the development of nausea and vomiting.

In **Dinesh Sahu** et al's [13] study, 10% patients in Ephedrine and Phenylephrine group and 15% patients in Mephentermine group developed nausea and vomiting. **Moran DH** et al [14] also found that there were no significant differences between the Ephedrine, Phenylephrine groups in the frequency of maternal nausea and vomiting. In **Turkoz A** et al's [38] study nausea was observed in one patient (6%) in the Ephedrine infusion group and nausea and vomiting were observed in 10 patients (66%) in the Ephedrine bolus group.

Neonatal outcome:

Casey et al [24] on their retrospective analysis found that Apgar score is comparable to umbilical artery pH in predicting the neonatal outcome. On assessing the Apgar score in our study two neonates had Apgar of 6 in group-I and II and one neonate in group-III. At 5 mt, no neonate had an Apgar score of less than 7 in all three groups. **Moran** et al [14] reported in their study with one neonate with an Apgar of less than 7 in Ephedrine group compared with no neonate in the Phenylephrine group. However at 5 mts, no neonate in the Ephedrine or Phenylephrine groups had an Apgar of less than 7.In the studies done by **Thomas** et al [17], Hall PA et al [39], **Alahutta** et al [40], **Laporta** et al [15], **Ayorinde** et al [30] also same results were obtained. All the neonates had an Apgar of more than 7 at 5 mts in both Ephedrine and Phenylephrine group. In the study done by **Dinesh Sahu** et al [13] on comparing Ephedrine, Mephentermine and Phenylephrine; they found no untoward effects on fetal outcome. In all the three groups the entire neonate had an Apgar of 7 and more than 7 at 1st and 5th minute. **Kansai** et al [23] on comparing the effects of

IV infusion of Ephedrine and Mephentermine found that neonatal Apgar scores are comparable in both the groups.

Dosage requirements:

In Group-I: 70% of patients required one, 27% of patients required two and 3% of patients required three bolus doses to maintain systolic pressure within 20%limit of basal value. In Group-II: 77% of patients required one and 23% of patients required two bolus doses to maintain systolic pressure within 20%limit of basal value. In Group-III: 90% of patients required one and 10% of patients required two doses to maintain systolic pressure within 20%limit of basal value. Phenylephrine was most effective in treating hypotension followed by Mephentermine and then by Ephedrine.

Similar results were seen in the study done by **Dinesh Sahu** et al [13] with Phenylephrine being most effective in treating hypotension on comparing with Mephentermine and Ephedrine. **Thomas DG** et al [17] concluded that in Ephedrine and Phenylephrine groups median (range) number of boluses of Ephedrine and Phenylephrine was similar. **Kansai A** et al [23] compared the effects of IV infusions of Ephedrine and Mephentermine and found that the amount of vasopressor required were statistically similar in both groups.

Thus all the vasopressors effectively maintained the pressures within 25% of baseline values; Phenylephrine maintained it effectively with fewer doses followed by Mephentermine and Ephedrine.

SUMMARY

This double blind prospective randomized control study was designed to evaluate the efficacy of Ephedrine, Mephentermine and Phenylephrine in treating hypotension during spinal anaesthesia for cesarean section. The incidence of undesirable side effects and neonatal outcome in terms of Apgar score were also studied.

Following observations were made:

1. All the three vasopressors maintained the arterial pressure effectively within 20% of baseline values.
2. The mean value of heart rate was highest in Mephentermine group followed by Ephedrine and Phenylephrine groups.
3. The mean values of Systolic BP, Diastolic BP and MAP were higher in Phenylephrine group followed by Mephentermine group and Ephedrine group throughout the study period.
4. Phenylephrine group required fewer number of bolus doses when compared with Mephentermine and Ephedrine group.
5. The heart rate generally remained low throughout the study period in Phenylephrine group and the incidence of bradycardia was more in Phenylephrine group when compared with other two groups.
6. The incidences of tachycardia were same in both Ephedrine and Mephentermine groups (one case in each group).In Ephedrine group two cases developed hypertension compared with no hypertension in other two groups. The occurrence of nausea and vomiting were similar and comparable in all the three groups.
7. In all the three groups no neonate had an Apgar score of less than 7 at 5^{th} minute.

CONCLUSION

In conclusion, we found that all the three vasopressors namely Ephedrine, Mephentermine and Phenylephrine are effective in IV bolus form in maintenance of maternal arterial pressure within 20% limit of baseline values, though Phenylephrine has quicker peak effect, in comparison to Ephedrine and Mephentermine and it causes reduction in heart rate, which may be advantageous in patients in whom tachycardia is undesirable. All the three vasopressor had no significant adverse effects on neonatal outcome.

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COMPARISION OF BOLUS EPHEDRINE, MEPHENTERMINE PHENYLEPHRINE FOR THE MANAGEMENT OF HYPOTENSION DURING SPINAL ANAESTHESIA FOR CAESAREAN SECTION-A CLINICAL STUDY

Patient details: Date:
Name/IP No:
ASA:
Age
Indication:
Weight:
G P L A :
Study group:

Investigation:

Hb%:	VP(GIVEN)	2	4	6	8	10	15	20	25	30
PCV:										
Blood Grouping:										
Premedication:										
Elective surgery: Emergency Surgery:										

T.Ranitidine: 150mg PO Inj Ranitidine: 50 mg IV T.Metaclopramide: 10mg PO Inj Metaclopramide: 10 mg IV -2 hrs before elective surgery -30 mts before emergency surgery. Preloading: • Ringer Lactate: 15 ml/kg Base line values: HR: SAB: Position: Space:										
HR										
SBP										
DBP										
MAP										
SPO_2										

Hypotension: Bradycardia:

Time of onset SAB			Time of onset	
Lowest Sys BP recorded			After SAB	
Total no of Boluses			After VP	
Total dose of VP used			Treated with	

APGAR Score:

First minute			Total IVF	
5th minute				
Tachycardia: Hypertension: Time of onset				
After SAB				
After VP				
Timing: SAB				
Incision				
Delivery				
Onset: Nausea				
vomiting			U/O	